National Library of Canada
Bibliothèque nationale du Canada

Acquisitions and Bibliographic Services Branch
Direction des acquisitions et des services bibliographiques

395 Wellington Street
Ottawa, Ontario
K1A 0N4

395, rue Wellington
Ottawa (Ontario)
K1A 0N4

Your file Votre référence

Our file Notre référence

NOTICE

The quality of this microform is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us an inferior photocopy.

Reproduction in full or in part of this microform is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30, and subsequent amendments.

AVIS

La qualité de cette microforme dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de qualité inférieure.

La reproduction, même partielle, de cette microforme est soumise à la Loi canadienne sur le droit d'auteur, SRC 1970, c. C-30, et ses amendements subséquents.

Canada

UNIVERSITY OF ALBERTA

REDUCED PYRIDINE ANALOGS AS NONSTEROIDAL ANTIINFLAMMATORY DRUGS

BY

SAMMY ASIAMAH AGUDOAWU

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of **DOCTOR OF PHILOSOPHY**.

IN

PHARMACEUTICAL SCIENCES
(MEDICINAL CHEMISTRY)

FACULTY OF PHARMACY AND PHARMACEUTICAL SCIENCES

EDMONTON, ALBERTA

FALL 1993

National Library of Canada
Acquisitions and Bibliographic Services Branch
395 Wellington Street
Ottawa, Ontario
K1A 0N4

Bibliothèque nationale du Canada
Direction des acquisitions et des services bibliographiques
395, rue Wellington
Ottawa (Ontario)
K1A 0N4

Your file Votre référence

Our file Notre référence

The author has granted an irrevocable non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of his/her thesis by any means and in any form or format, making this thesis available to interested persons.

L'auteur a accordé une licence irrévocable et non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de sa thèse de quelque manière et sous quelque forme que ce soit pour mettre des exemplaires de cette thèse à la disposition des personnes intéressées.

The author retains ownership of the copyright in his/her thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without his/her permission.

L'auteur conserve la propriété du droit d'auteur qui protège sa thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

ISBN 0-315-88335-9

Canada

UNIVERSITY OF ALBERTA

RELEASE FORM

NAME OF AUTHOR: **SAMMY ASIAMAH AGUDOAWU**

TITLE OF THESIS: **REDUCED PYRIDINE ANALOGS AS NON-STEROIDAL ANTIINFLAMMATORY DRUGS**

DEGREE: **DOCTOR OF PHILOSOPHY**

YEAR THIS DEGREE GRANTED: **1993**

Permission is hereby granted to the University of Alberta Library to reproduce single copies of this thesis and to lend or sell such copies for private, scholarly or scientific research purposes only.

The author reserves all other publication and other rights in association with the copyright in the thesis, and except as herein before provided neither the thesis nor any substantial portion thereof may be printed or otherwise reproduced in any material form whatever without the author's prior written permision.

Sammy Agudoawu

SAMMY A GUDOAWU

81 RIDGEWOOD TERRACE, ST. ALBERT, AB, T8N 0B1

DATED 17TH AUGUST , 1993

Dedicated to

Antoinette my wife

UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled **REDUCED PYRIDINE ANALOGS AS NONSTEROIDAL ANTIINFLAMMATORY DRUGS** submitted by **SAMMY ASIAMAH AGUDOAWU** in partial fulfillment of the requirements for the degree of **DOCTOR OF PHILOSOPHY** in **PHARMACEUTICAL SCIENCES (MEDICINAL CHEMISTRY)**.

E. E. Knaus

Dr. E. E. Knaus (Supervisor)

R. Moskalyk

Dr. R. E. Moskalyk

F. M. Pasutto

Dr. F. M. Pasutto

D. L. J. Clive

Dr. D. L. J. Clive

M. Daneshtalab

Dr. M. Daneshtalab

J. R. Dimmock

Dr. J. R. Dimmock, External Reader

Dated July 27, 1993

ABSTRACT

The synthesis and pharmacological evaluation of novel dihydropyridines as analgesic-antiinflammatory agents have been investigated.

The regiospecific copper catalyzed reduction of the 3-benzoyl-N-substituted pyridinium salts **88** and **89** by a Grignard reagent (RMgCl) afforded the corresponding 3-benzoyl-4-substituted-1,4-dihydropyridyl-1-acetic acid esters (**90-93**). Alkaline hydrolysis of **90-93** using aqueous sodium hydroxide and then acidification with 5 N hydrochloric acid gave the acids **97a-98e**. The 3-benzoyl-1,4-dihydropyridylacetamides **99** were synthesized by ammonolysis of **90-93**. The 3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl-1-acetic acid esters (**103**, **104**), acetamides (**105**, **106**) and acetic acids (**107**, **108**) were also synthesized in an effort to selectively synthesize the physiologically more active enantiomers since a large proportion of the traditional NSAIDs, having an α-methyl acetic acid side chain have one chiral center and the S(+)-enantiomers are generally the most active.

Methyl 2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**111**) and methyl 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**112**) were also synthesized in further efforts to prepare two diastereomers which could be separated (from **111**) or a single enantiomer (from **112**) for evaluation as antiinflammatory agents. Compound **113** was synthesized by catalytic hydrogenation of **91b**.

Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (**125-128**) were synthesized from **91** and the dihalo carbene transfer reagent $PhHgCX_3$ (X = F, Cl, Br). Monodehalogenation of these gem-dihalocyclopropanes with tri-*n*-butyltin hydride afforded methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (**129-131**). Methyl 2-methyl-2-[1-(3-phenoxy-4-phenyl-1,4-dihydropyridyl)]acetate **146** was synthesized from the N-substituted 3-phenoxypyridinium salt **145** and phenylmagnesium chloride in the presence

of cuprous iodide but this compound was found to be unstable and decomposed on storage.

Ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]acetates **149-152** were synthesized from their N-acylpyridinium salts prepared *in situ* from ethyl 3-pyridyl-acetate and subsequent phenyl chloroformate copper-catalyzed Grignard reduction. Ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate **153** was also synthesized from ethyl 2-methyl-3-pyridylacetate and phenyl chloroformate followed by Grignard reaction with phenyl magnesium chloride.

Further efforts directed towards the synthesis of chiral N-substituted 1,4-dihydropyridyl acetic acid analogs led to the synthesis of 3-benzoyl-4-phenyl-1-{1-methyl-2-oxo-2-[(4S)-4-isopropyl-2-oxazolidinoyl]ethyl}-1,4-dihydropyridine (**135**), N-[(1S)-1-phenethyl-2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridine)]acetamide diastereomers (**137a**, **137b**), (S)-methoxycarbonyl-α-methyl methyl 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetate **138** and (4S)- or (4R)-methyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (**143**).

The analgesic activities for compounds **90-93**, **96**, **97-98**, **99**, **103-108**, **111**, **112**, **113**, **125-132**, **149-152**, **153**, and **154** were determined using the 4% sodium chloride writhing assay in rats, while their antiinflammatory activities were determined by the carrageenan-induced edema rat paw assay. The pharmacological results indicated that the C-4 phenyl substituent of the 1,4-dihydropyridyl ring was a determinant of activity and likewise the α-methyl substituent of the N-acetyl moiety.

The ulcerogenic liability of compounds **91a**, **98a** and **99d** were determined and were found to be non-ulcerogenic compared to Ibuprofen which had a UD_{50} of 250 mg/kg po. The pK_a of compound **98a** was also determined and found to be 9.2.

ACKNOWLEDGEMENTS

My sincere gratitude is hereby expressed to my supervisor, Dr. E. E. Knaus for his guidance and encouragement during the course of my study. I thank A. Wiseman who typed this thesis and also Carol-Anne McEwen who assisted with the word processing. I also wish to thank Dr. Dean Vo, Dr. John Wei, and Dr. P. Kumar for their assistance in preparing this thesis. Finally, I acknowledge the Canadian Commonwealth Scholarship Committee for a studentship award and the Medical Research Council of Canada (Grant MT-4888) which enabled me to pursue this study.

TABLE OF CONTENTS

1.0.0.0.0.0.	INTRODUCTION	1
1.1.0.0.0.0.	NONSTEROIDAL ANTIINFLAMMATORY DRUGS	2
1.1.1.0.0.0.	Aryl and Heteroarylcarboxylic Acids	2
1.1.2.0.0.0.	Enolic Acids with Antiinflammatory Activity	6
1.1.3.0.0.0.	Pyridyl and Dihydropyridyl Acetic Acid Analogs of NSAIDs	8
1.1.4.0.0.0.	Selective and/or Dual Inhibitors of 5-Lipoxygenase and Cyclooxygenase	11
1.2.0.0.0.0.	THE ORIGIN OF INFLAMMATION	13
1.3.0.0.0.0.	STRUCTURE-ACTIVITY RELATIONSHIPS FOR NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDs)	15
1.4.0.0.0.0.	SELECTIVITY OF NSAIDs	21
1.5.0.0.0.0.	THE PHARMACOLOGY OF PYRIDINES AND DIHYDROPYRIDINES	23
1.5.1.0.0.0.	The Chemistry of Dihydropyridines	25
1.5.2.0.0.0.	Synthesis of Dihydropyridines	25
1.5.3.0.0.0.	Synthesis of Dihydropyridines Using Nucleophilic Organometallic Reagents	26
1.5.4.0.0.0.	Synthesis of Chiral α-Arylpropanoic Acids	28
1.5.5.0.0.0.	Hydrogenation of 2-Arylpropenoic Acids	28
1.5.6.0.0.0.	Sharpless Epoxidation	29
1.5.7.0.0.0	Grignard Coupling Reactions	30
1.5.8.0.0.0.	Enantioselective Protonation	31
2.0.0.0.0.0.	OBJECTIVES OF THE RESEARCH	33
3.0.0.0.0.0	RESULTS AND DISCUSSION	36
3.1.0.0.0.0.	SYNTHESES	36

3.1.1.0.0.0. Synthesis of 3-Benzoyl-4-substituted-1,4-dihydropyridyl-1-acetic acid esters (**90-93**), Acetic acids (**97-98**) and Acetamides (**99**) 36

3.1.2.0.0.0. Synthesis of 2-Methoxyphenyl 2-methyl-2-[1-(4-phenyl-3-benzoyl-1,4-dihydropyridyl)acetate (**96**) 66

3.1.3.0.0.0. Synthesis of 3,5-Dibenzoyl-4-phenyl-1,4-dihydropyridyl-1-acetic acid esters (**103** and **104**), Acetamides (**105** and **106**), and Acetic acids (**107** and **108**) 67

3.1.4.0.0.0. Ionization Constant Determination 73

3.1.5.0.0.0. Synthesis of Methyl 2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**111**) and Methyl 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**112**) 74

3.1.6.0.0.0. Synthesis of Methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydropyridyl)]acetate (**113**) 79

3.1.7.0.0.0. Synthesis of Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (**125-128**), Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (**129-131**), and 2-Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dibromo-2-azabicyclo-[4.1.0]hept-3-ene)]acetamide (**132**) 83

3.1.8.0.0.0. Attempted Synthesis of Chiral N-Substituted 1,4-Dihydropyridyl Analogs 98

3.1.9.0.0.0. Synthesis of 3-Benzoyl-4-phenyl-1-{1-methyl-2-oxo-2-[(4S)-4-isopropyl-2-oxazolidinonyl]ethyl}-1,4-dihydropyridine (**135**) 98

3.1.10.0.0.0. Synthesis of N-[(1S)-1-phenethyl]-2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide Diastereomers (**137a** and **137b**)..... 100

3.1.11.0.0.0. Synthesis of (S)-Methoxycarbonyl-α-methyl methyl-2-methyl-2-{1-[3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl]acetate (**138**)..... 100

3.1.12.0.0.0. Synthesis of (4S)- or (4R)-Methyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (**143**)..... 103

3.1.13.0.0.0. Attempted Synthesis of Methyl 2-methyl-2-[1-(3-phenoxy-4-phenyl-1,4-dihydropyridyl)]acetate (**146**)..... 105

3.1.14.0.0.0. Synthesis of Ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]acetates (**149-152**), Ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (**153**), and Ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (**154**)..... 107

3.2.0.0.0.0. PHARMACOLOGICAL SCREENS..... 112

3.2.1.0.0.0. Analgesic-Antiinflammatory Structure Activity Relationships (SARs) for Methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates (**90a-c**), Methyl 2-methyl-2-[(1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates (**91-93**), 2-[1-(3-Benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acids (**97a-c**), 2-Methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acids (**98a-e**), Methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetamides (**99a-c**), and 2-Methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]-acetamides (**99d-j**)..... 112

3.2.2.0.0.0. Analgesic-Antiinflammatory SARs of Methyl (**103**) and Methyl 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]-acetates (**104**), 2-[1-(3,5-Dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (**105**), 2-Methyl 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (**106**) and 2-[1-(3,5-Dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acids (**107** and **108**) 115

3.2.3.0.0.0. Analgesic-Antiinflammatory Activity of Methyl 2-methyl-2-(1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydropyridyl)]acetate (**113**) 120

3.2.4.0.0.0. Analgesic-Antiinflammatory Activity of Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (**125-128**) 123

3.2.5.0.0.0. Analgesic-Antiinflammatory SARs for Ethyl 2-[3-(1-phenoxy-carbonyl-4-substituted-1,4-dihydropyridyl)]acetates (**151-152**), Ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (**153**) and Ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (**154**) 123

3.3.0.0.0.0. ANALGESIC ACTIVITY EVALUATION 127

3.4.0.0.0.0. ANTIINFLAMMATORY ACTIVITY EVALUATION 128

3.5.0.0.0.0. ULCEROGENIC LIABILITY DETERMINATION 129

4.0.0.0.0.0. EXPERIMENTAL 131

4.1.0.0.0.0. PHYSICAL CONSTANTS AND SPECTROSCOPY 131

4.2.0.0.0.0. CHROMATOGRAPHY 131

4.3.0.0.0.0. SOLVENTS AND REAGENTS 131

4.4.0.0.0.0. SYNTHETIC CHEMISTRY 132

4.4.1.0.0.0. Methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]-acetates and Methyl 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates (**90-93**). General Procedure A 132

4.4.1.1.0.0. *o*-Methoxyphenyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (**96**) 133

4.4.2.0.0.0. 2-[1-(3-Benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acids and 2-Methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acids (**97-98**). General Procedure B 134

4.4.3.0.0.0. 2-Methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)acetamides (**99**). General Procedure C 134

4.4.3.1.0.0. 3,5-Dibenzoylpyridine (**100**) 135

4.4.4.0.0.0. Methyl 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]-acetate (**103**). General Procedure D 135

4.4.4.1.0.0. 2-[1-(3,5-Dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamides (**105** and **106**) 136

4.4.4.2.0.0. 2-[1-(3,5-Dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acids (**107** and **108**) 136

4.4.4.4.3.0. Methyl 2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)methyl]-acrylate (**111**) and Methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**112**) 137

4.4.4.4.0.0. Methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydropyridyl)acetate (**113**) 138

4.4.4.5.0.0. Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dibromo-2-azabicyclo[4.1.0]hept-3-ene]acetate (**125**) and Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dichloro-2-azabicyclo[4.1.0]hept-3-ene]acetate (**126**) 138

4.4.4.6.0.0 Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-difluoro-2-aza- 139
bicyclo[4.1.0]hept-3-ene)]acetate (**127**) and Methyl 2-methyl-
2-[2-(4-benzoyl-5-phenyl-7-chloro-7-fluoro-2-azabicyclo-
[4.1.0]hept-3-ene)]acetate (**128**)

4.4.4.7.0.0. Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabi-
cyclo[4.1.0]hept-3-ene)]acetates (**129**, 7-Br; **130**, 7-Cl; **131**,
7-F)..... 139

4.4.4.8.0.0. 2-Methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dibromo-2-azabicy-
clo[4.1.0]hept-3-ene)]acetamide (**132**)..... 140

4.4.4.9.0.0. 3-Benzoyl-4-phenyl-1-{1-methyl-2-oxo-2-[(4S)-4-isopropyl-2-
oxazolidinonyl]ethyl}-1,4-dihydropyridine (**135**) 140

4.4.4.10.0.0. N-[(1S)-1-phenethyl]-2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-
1,4-dihydropyridyl)]acetamide Diastereomers (**137a** and
137b)..... 141

4.4.4.11.0.0. (S)-Methoxycarbonyl-α-methyl methyl 2-{1-[3,5-dibenzoyl-4-
phenyl-1,4-dihydropyridyl]}acetate (**138**)..... 142

4.4.4.12.0.0. 3-Benzoyl-4-phenylpyridine (**140**)..... 142

4.4.4.13.0.0. Attempted Synthesis of (4S)- or (4R)-Methyl 2-methyl-2-[1-(3-
benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (**143**)..... 143

4.4.4.14.0.0. Methyl 2-methyl-2-[1-(3-phenoxy-4-phenyl-1,4-dihydropyr-
idyl)]acetate (**146**)..... 143

4.4.5.0.0.0. Ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydropyr-
idyl)]acetates (**149-152**), Ethyl 2-methyl-2-[3-(1-phenoxy-
carbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (**153**) and Ethyl
2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate
(**154**). General Procedure D..... 144

4.5.0.0.0.0. DETERMINATION OF THE pKa VALUE FOR 2-METHYL-2-[1-(3-BENZOYL-4-PHENYL-1,4-DIHYDROPYRIDYL)]-ACETIC ACID (**98a**) 145
4.6.0.0.0.0. ANALGESIC ACTIVITY ASSAY 146
4.7.0.0.0.0. ANTIINFLAMMATORY ACTIVITY ASSAY 147
4.8.0.0.0.0. ULCEROGENIC LIABILITY ASSAY 147
5.0.0.0.0.0. REFERENCES 149

LIST OF TABLES

Table 1. Interatomic distances (Å), bond angles (°), torsion angles (°) and local minimum energy (kcal/mol) 42

Table 2. IR and ^{1}H NMR spectral data for methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates **90a-90c**; methyl 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates **91a-91h**, **92a-92d**, **93**; *ortho*-methoxyphenyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate **96**; 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acids **97a-97c**; 2-methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acids **98a-98e**; 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetamides **99a-99c**; and 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetamides **99d-99j** 46

Table 3. Physical data for methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates **90a-c**, methyl 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates **91-93**; 2-methoxyphenyl-2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate **96**; 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acids **97a-c**; 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acids **98a-e**; 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetamides **99a-c**; and 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetamides **99d-j** 62

Table 4. IR and ^{1}H NMR spectral data for methyl (**103**) and methyl 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetates (**104**), 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (**105**), 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (**106**) and 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acids (**107** and **108**)..... 69

Table 5. Physical data for methyl (**103**) and methyl 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetates (**104**), 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (**105**), 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (**106**) and 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acids (**107** and **108**)..... 71

Table 6. Data for the potentiometric titration of 0.01 M methanolic solution of 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acid (**98a**) with a 0.10 M potassium hydroxide solution in water:methanol (60:40, v/v)..... 75

Table 7. IR and ^{1}H NMR data for methyl 2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**111**), methyl 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**112**), and methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydropyridyl)]acetate (**113**)..... 76

Table 8. Physical data for methyl 2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**111**), methyl 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**112**), and methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydropyridyl)]acetate (**113**)..... 78

Table 9. IR and ^{1}H NMR spectral data for methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]-hept-3-ene)]acetates (**125-128**), methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo[4.1.0]-hept-3-ene)]acetates (**129-131**) and acetamide (**132**) 85

Table 10. Physical data for methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]-hept-3-ene)]acetates (**125-128**), methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo[4.1.0]-hept-3-ene)]acetates (**129-131**) and acetamide (**132**) 91

Table 11. ^{1}H NMR spectral data for N-[(1S)-1-phenethyl]-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide diastereomers (**137a** and **137b**) 101

Table 12. IR and ^{1}H NMR spectral data for ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]acetates (**149-152**), ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-1,4-dihydropyridyl)]acetate (**153**), and ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (**154**) 108

Table 13. Physical data for ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]acetates (**149-152**), ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-1,4-dihydropyridyl)]acetate (**153**), and ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (**154**) 111

Table 14. Pharmacological data for methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates **90a-90c**; methyl 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates **91a-91h**, **92a-92d**, **93**; *ortho*-methoxyphenyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate **96**; 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acids **97a-97c**; 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acids **98a-98e**; 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetamides **99a-99c**; and 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetamides **99d-99j** 116

Table 15. Pharmacological data for methyl (**103**) and methyl 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetates (**104**), 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (**105**), 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (**106**) and 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acids (**107** and **108**) 121

Table 16. Pharmacological data for methyl 2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**111**), methyl 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**112**), and methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydropyridyl)]acetate (**113**) 122

Table 17. Pharmacological data for methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (**125-128**), methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo-[4.1.0]hept-3-ene)]acetates (**129-131**) and acetamide (**132**) 124

Table 18. Pharmacological data for ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]acetates (**149-152**), ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-1,4-dihydropyridyl)]acetate (**153**), and ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (**154**)..... 126

LIST OF FIGURES

Figure 1. The Arachidonic acid cascade 15

Figure 2. Receptor model based on the chemical structure of Indomethacin..... 16

Figure 3. Receptor site for acidic NSAIDs constructed according to the probable conformation of the substrate Arachidonic acid (slightly modified) 17

Figure 4. Chemical structures of the peroxyradical of Arachidonic acid in its favored conformation (**39**), and of the NSAID (S)-2-(3-chloro-4-cyclohexylphenyl)propionic acid (**40**), Indomethacin (**41**), Ketoprofen (**42**), Fenoprofen (**43**), Alclofenac (**44**), Ibuprofen (**45**), and Naproxen (**46**), respectively..... 18

Figure 5. Common structural features of NSAIDs..... 20

Figure 6. Nuclear Overhauser Enhancement spectral data for methyl 2-methyl-2-[1-(4-phenyl-3-benzoyl-1,4-dihydropyridyl)]acetate **91a**.. 40

Figure 7. Nuclear Overhauser Enhancement spectral data for methyl 2-methyl-2-[1-(4-phenyl-3-benzoyl-1,4-dihydropyridyl)]acetate **91b**.. 40

Figure 8. Proposed conformation of a classical calcium antagonist of the 1,4-dihydropyridine type..... 41

Figure 9. Deactivation of C2-C3 conjugated double bond by resonance..... 83

Figure 10. Possible conformation of methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (**125-128**) 95

Figure 11. Most stable conformation of methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (**125-128**) 95

Figure 12. Most probable conformation of methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-difluoro-2-azabicyclo[4.1.0-]hept-3-ene)]acetate (**127**).. 96

Figure 13. Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-fluoro-7-chloro-2-azabicyclo[4.1.0]hept-3-ene)]acetate (**128**) diastereomer..... 96

Figure 14. Conformation of methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-chloro-2-azabicyclo[4.1.0]hept-3-ene)]acetate (**130**) and methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-fluoro-2-azabicyclo[4.1.0]-hept-3-ene)]acetate (**131**)..... 97

Figure 15. Rotamers of compound **153** as a result of restricted rotation..... 112

LIST OF SCHEMES

Scheme 1. Synthesis of methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates and methyl 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates (**90-93**); 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acids and 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acids (**97**, **98**); 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetamides and 2-methyl-2-[1-(3-benzoyl-1,4-substituted-1,4-dihydropyridyl)]-acetamides (**99**) 38

Scheme 2. Synthesis of 2-methoxyphenyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (**96**) 67

Scheme 3. Synthesis of 3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl-1-acetic acid esters (**103** and **104**), acetamides (**105** and **106**) and acetic acids (**107** and **108**) 72

Scheme 4. Synthetic route for the preparation of **111** and **112** 79

Scheme 5. Synthesis of methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydropyridyl)]acetate (**113**) 80

Scheme 6. Catalytic hydrogenation of 9-phenanthrol (**114**) 80

Scheme 7. Partial catalytic hydrogenation of the azepine (**116**) 81

Scheme 8. Partial hydrogenation of the 1-alkyl-3-benzoylpyridinium salt (**118**) to give the tetrahydropyridine (**119**) 81

Scheme 9. Preferential hydrogenation of the isolated C5-C6 double bond of (**120**) relative to the C2-C3 double bond 82

Scheme 10. Synthesis of methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (**125-128**), methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (**129-131**), and 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dibromo-2-azabicyclo[4.1.0]hept-3-ene)]acetamide (**132**)..... 93

Scheme 11. Synthesis of 3-benzoyl-4-phenyl-1-{1-methyl-2-oxo-2-[(4S)-4-isopropyl-2-oxazolidinonyl]ethyl}-1,4-dihydropyridine (**135**)..... 99

Scheme 12. Synthesis of N-[(1S)-1-phenethyl]-2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide diastereomers (**137a**) and (**137b**).....102

Scheme 13. Synthesis of (S)-methoxycarbonyl-α-methyl methyl-2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (**138**) 104

Scheme 14. Synthesis of (4S)- or (4R)-methyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (**143**) 105

Scheme 15. Synthesis of methyl 2-methyl-2-[1-(3-phenoxy-4-phenyl-1,4-dihydropyridyl)]acetate (**146**).....106

Scheme 16. Ethyl 2-[3-[(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]-acetates (**149-152**), ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (**153**) and ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (**154**) 107

1.0.0.0.0.0. INTRODUCTION

Arthritis is a family of joint diseases affecting 7% of the total population world-wide. Its impact on the well-being of patients and socioeconomic effects are widely recognized. The search for antiarthritic drugs to relieve swelling, redness, pain, and fever associated with inflammed joints, and to restore impaired physical functions, dates back to antiquity. Aspirin and sodium salicylate have been widely used for more than a century. However, modern chemical and pharmacological research to discover more effective and better tolerated antiarthritic drugs began to flourish in the late 1940's after the dramatic antirheumatic effect exhibited by corticosteroids was serendipidously discovered with a synthetic sample of hydrocortisone.[1] A decade of intensive steroid research during the 1950's produced many corticosteroid analogs with increased potency. However, attempts to reduce their hormonal and metabolic side effects were generally disappointing. Following this, a search for non-steroidal antiinflammatory drugs (NSAIDs) was initiated.

Rheumatoid arthritis, osteoarthritis and ankylosing spondylitis are three inflammatory diseases which affect more than 3 million Canadians over the age of 30 years. A significant number of adolescents between the ages of 10 - 15 years have also been diagnosed as arthritic individuals. Arthritis, unlike other diseases, is seldom fatal but it often progresses to a state resulting in severe pain, inflammation, and crippling effects. Health and Welfare Canada reported that the most prevalent health problems in Canada are related to arthritis, and other bone and joint disorders. These have been reported two times more frequently than mental disorders or cardiovascular diseases. As the population grows progressively older, antiarthritic and analgesic drugs will become increasingly important. The broad class of nonsteroidal antiinflammatory drugs (NSAIDs) are invaluable in the treatment of rheumatoid arthritis and osteoarthritis.[2]

1.1.0.0.0.0. NONSTEROIDAL ANTIINFLAMMATORY DRUGS

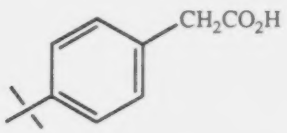
Cyclooxygenase-inhibiting NSAIDs, by blocking the production of prostaglandins from arachidonic acid ameliorate the primary symptoms of arthritis via their analgesic, antipyretic, and antiinflammatory effects. However, NSAIDs do not prevent tissue destruction or stop the disease process.[3] Leukotrienes, the products of 5-lipoxygenase (5-LO) metabolism of arachidonic acid, have been associated with immediate hypersensitivity and asthmatic reactions.[4] 5-LO metabolites have also been linked to the inflammatory process. These metabolites have been shown to stimulate neutrophil degranulation[5] resulting in the release of lysosomal enzymes and reactive oxygen species and to increase capillary permeability[6] thereby contributing to edema. These responses suggest a significant role for 5-LO metabolites in the initiation and amplification of the inflammatory response. Therefore a dual cyclooxygenase/lipoxygenase (CO/LO) inhibitor would influence a wider range of proinflammatory mechanisms and presumably have an improved profile.

1.1.1.0.0.0. Aryl and Heteroarylcarboxylic Acids

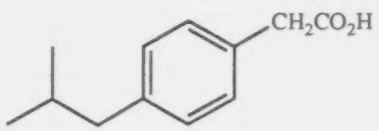
Without doubt, the aryl- and heteroarylcarboxylic acids have been one of the most widely explored groups of nonsteroidal compounds as potential antiinflammatory agents. The origin of a significant percentage of this interest in aryl and heteroarylcarboxylic acid antinflammatory agents can be traced to the pioneering work in the early 1960's by the Boots Pure Drug Company in England. From a large group of 4-alkyl-, 4-cycloalkyl-, 4-alkoxy-, 4-phenylthio-, and 4-phenoxyphenyl acetic acids investigated, the 4-t-butyl compound (**1**), was selected for clinical trials. This compound, RD10335, was effective for the treatment of rheumatoid arthritis, but a significant proportion of patients developed a skin rash which terminated further study.[7]

Although Ibufenac (**2**) was 2 - 4 fold more potent than Aspirin,[8] it was subsequently withdrawn from clinical use due to hepatotoxicity. It was later found that the α-methyl

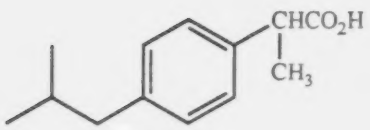
analog of Ibufenac, which was named Ibuprofen (**3**), exhibited relatively weak activity against established adjuvant arthritis in rats, but it demonstrated good activity in other antiinflammatory, analgesic, and antipyretic tests in animals.[9]



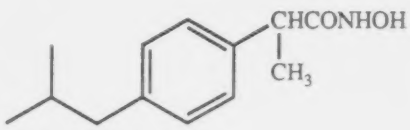
1



2



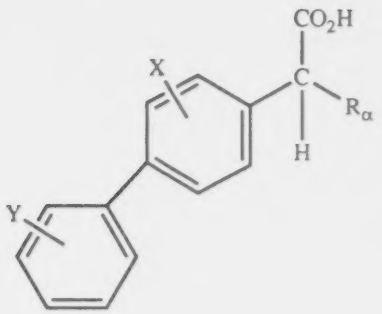
3



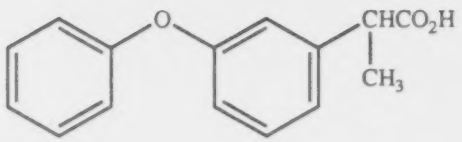
4

The primary metabolites of Ibuprofen, isolated from human plasma and urine after oral administration of the racemate, possess predominantly the (S)-(+) configuration. The inversion of configuration has now been shown to be due to biotransformation of the (R)-(-) enantiomer to the (S)-(+) enantiomer in vivo.[10,11] The hydroxamic acid derivative of Ibuprofen, Ibuproxam (**4**), also exhibits good antiinflammatory, analgesic and antipyretic activities in animals with minimal gastrointestinal side effects.[12] Ibuproxam provided significantly higher plasma concentrations of Ibuprofen in human volunteers than an equal dose of the carboxylic acid, and the effective plasma half-life of Ibuprofen was extended slightly.[13] The improved availability of Ibuproxam may be due to its pK_a of 8.68, which results in less dissociation relative to Ibuprofen with a pK_a of 5.41 at the gastric pH of 1.5, thereby producing enhanced absorption. The activity of Ibuproxam has been ascribed to both intact parent molecule and its metabolite Ibuprofen.[13] There is a great deal of interest in Flurbiprofen (**5**, $R_\alpha = CH_3$, X = 3-F, Y = H) which elicits potent antiinflammatory, analgesic and antipyretic effects. It is ten times more potent than Ibuprofen in most test systems,[14] and is claimed to be >5000 times more potent than Indomethacin in its ability to

inhibit prostaglandin synthetase using a microsomal fraction from human rheumatoid synovial cells.[15]

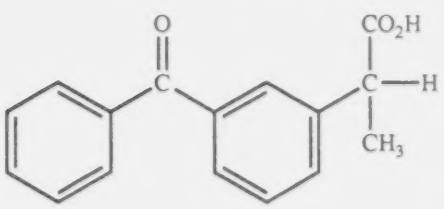


5

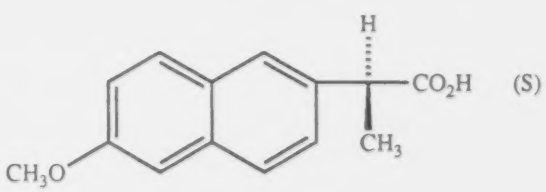


6

The racemate of α-methyl-3-phenoxyphenylacetic acid, (Fenoprofen, **6**) was reported to be active in the carrageenan induced rat paw edema assay, to have an ED_{50} of 0.5 - 1.0 mg/kg in the UV erythema assay in the guinea pig and to exhibit antiinflammatory, antipyretic and peripheral analgesic activities. Molecular modification of known phenothiazine/alkanoic acids prompted the synthesis of racemic 3-benzoyl-α-methyphenyl acetic acid (Ketoprofen, **7**) which was the most potent member of a group of related analogs that shared comparable activity to Indomethacin in the carrageenan-induced rat paw edema assay. However, in rats, it was one of the most ulcerogenic compounds in this series.[16]



7

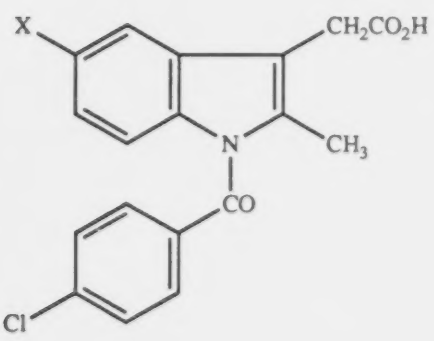


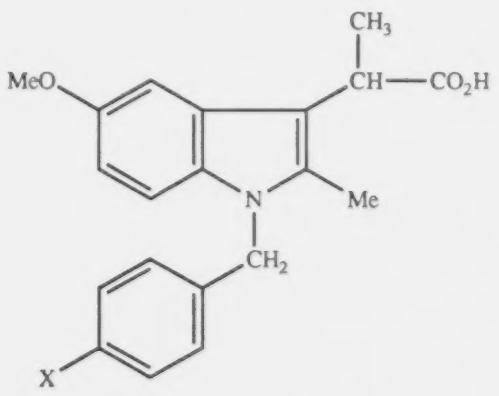
(S)

8

A series of 2-naphthaleneacetic acids was found to possess antiinflammatory, analgesic and antipyretic activities. The antiinflammatory activity of the lead compound, 2-naphthaleneacetic acid was enhanced by introducing a small lipophilic substituent such as OCH_3, SCH_3 or Cl at C-6, and by elaboration of the carboxyl to a methyl ester group.[17] The (S)-(+)-enantiomer of Naproxen (**8**), exhibited a potency 11 times that of phenylbutazone in the carrageenan-induced rat paw edema assay.[17] Naproxen is the only antiinflammatory carboxylic acid marketed as a single enantiomer, where the (S)-(+)-enantiomer is substantially more potent than the (R)-(-)- enantiomer in both the paw edema antiinflammatory screen and a yeast-induced antipyresis model in rats.[17] Naproxen is superior to Ibuprofen for pain reduction and relief from morning stiffness.[18]

Indomethacin (**9**), was developed as a result of a systematic study by Merck, Sharp and Dohme to examine indole and indene derivatives as potential antiinflammatory agents.[19] The initial test results prompted the selection of two, 2-(1-substituted benzyl-5-methoxy-2-methylindol-3-yl)propionic acids as clinical candidates. Although the racemic 4-chlorobenzyl analog (**10**) and the (+) -enantiomer of the 4-methylthiobenzyl analog (**11**) were effective in patients, gastrointestinal irritation was induced.[20]

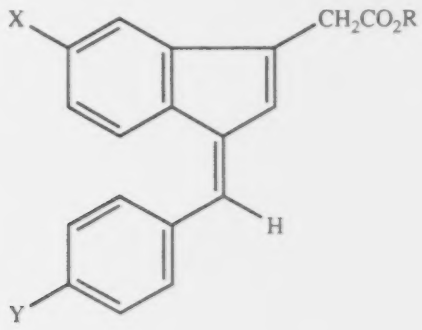




9, X = CH_3 **10**, X =Cl

12, X = $(CH_3)_2N$ **11**, X =SCH_3

Further modifications led to the selection of Indomethacin, its 5-dimethylamino analog (**12**) and the indene isostere (**13**) as clinical antiinflammatory drug candidates.



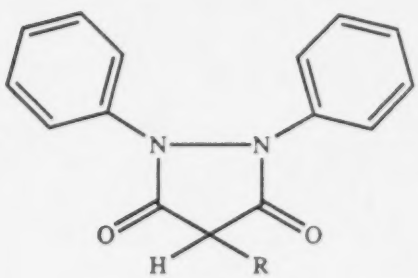
	X	Y	R
13,	CH_3O	OH	H
14,	F	CH_3SO	H
15,	F	CH_3S	H

A new derivative, Sulindac (**14**) was later introduced as a pro-drug that is nearly devoid of intrinsic pharmacological activity. It is metabolised o the sulfide (**15**), which is the active pharmacophore that possesses potent antiinflammatory, analgesic, antipyretic, prostaglandin cyclooxygenase inhibitory and hydroxyl radical scavenging activity. The sulfide is more ulcerogenic in rats than the sulfoxide. Administration of the pro-drug causes less gastrointestional (GIT) irritation than does the sulfide.[21] X-ray, NMR, and CNDO/2 calculations have shown that the N-benzoyl group of Indomethacin is tilted away from the C-2 methyl substituent, and that it is out of the plane of the indole nucleus. A similar stereochemistry has been observed for Sulindac,[22] and its active sulfide metabolite. (Z)-Indenes exhibit good antiinflammatory activity, whereas the (E)-isomers exhibit marginal activity.[23]

1.1.2.0.0.0. Enolic Acids with Antiinflammatory Activity

Phenylbutazone (**16**), was first synthesised in 1946.[24] It was withdrawn from clinical use since it caused undesirable bone marrow aplasia, peptic ulceration and fluid retention side effects. A number of phenylbutazone analogs were subsequently synthesised in an

attempt to increase activity and reduce toxicity. Modification of the *n*-butyl substituent provided analogs with a variety of clinical properties. The 2-phenylthioethyl compound (**17**) was a less effective antiinflammatory agent and a more potent uricosuric agent than phenylbutazone.[25] The corresponding sulfoxide (**18**, Sulfinpyrazole), which exhibited weak antiinflammatory activity, provided useful uricosuric and platelet inhibition properties.[26,27] The latter compound **18** is used clinically for the treatment of acute gout and for the prevention of cardiac mortality following recent myocardial infarction. When the *n*-butyl group was replaced by one, two, or three isoprene moieties joined in a head-to-toe manner, a series of analogs was obtained that exhibited antiinflammatory and analgesic properties in conjuction with a degree of ulcerogenicity in animals. The most interesting compound in this group was Feprazone (**19**), which was shown in clinical trials to be effective for the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondiylitis with minor gastrointestinal side effects.[28]

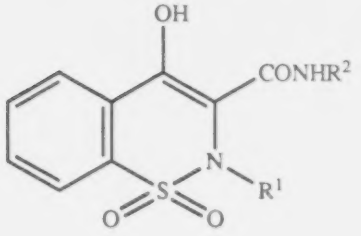


	R
16,	$-(CH_2)_3CH_3$
17,	$-(CH_2)_2SC_6H_5$
18,	$-(CH_2)_2SOC_6H_5$
19,	$-CH_2CH=C(CH_3)_2$

Physiological disposition and physicochemical property data such as pK_a value, partition coefficient, solubility, plasma binding, half-life and tissue distribution values have been reviewed for a number of phenylbutazone analogs,[29-35] in an attempt to derive correlations with clinical data. Compounds with pK_a values in the 4.5-5.5 range possess long plasma half-lives, more potent antiarthritic activities and less potent uricosuric properties. The more acidic analogs, particularly those with pK_a values below 3, tend to

have short half-lives, weak antiarthritic activities, and potent uricosuric effects. Analogs with pK_a values higher than 5.5 such as the cyclopentanedione and cyclopentenedione isosteres of phenylbutazone, were inactive antiinflammatory agents. The potent uricosuric properties of the highly acidic analogs has been attributed to the ionic species (enolic acid) of these drugs that block reabsorption of uric acid by the renal tubules.[29]

Piroxicam (**20**), is a member of a novel class of enolic acids that is the most potent nonsteroidal drug available for the treatment of human inflammatory diseases.



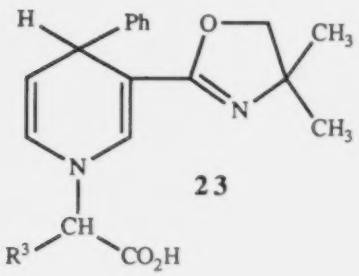
	R^1	R^2
20,	CH_3	2-pyridyl
21,	CH_3	2-thiazolyl
22,	CH_3	5-methyl-2-isoxazolyl

World-wide clinical trials have shown that Piroxicam is effective for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, gout, musculoskeletal pain and various pain states. The most frequently reported effect of Piroxicam is gastrointestinal intolerance.[36,37] Susoxicam (**21**), a close relative of Piroxicam, has been reported to be effective in rheumatoid arthritis.[38] Isoxicam (**22**) is now in Phase III clinical trials.[39]

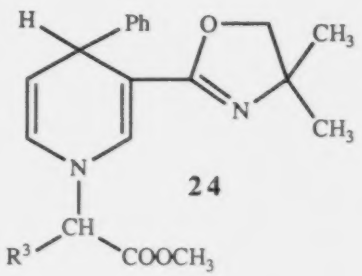
1.1.3.0.0.0. Pyridyl and Dihydropyridyl Acetic Acid Analogs of NSAIDs

Kumar and Knaus,[40] have synthesised a series of N-substituted-1,4-dihydropyridylacetic acids (**23**), acetic acid esters (**24**), and acetamides (**25**) as potential antiinflammatory agents. The presence of a R^3-methyl substituent, and increasing the length of the alkyl ester moiety, both enhanced antiinflammatory activity. The relative order of antiinflammatory potency was generally ester > amide > acid. Methyl 2-methyl-2-{1-[4-phenyl-3-(4,4-dimethyloxazolin-2-yl)-1,4-dihydropyridyl]}acetate (**24**), was the most active antiinflammatory agent in this series, reducing inflammation 73.9% at 3 hours

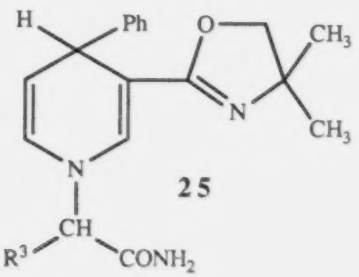
after a 100 mg/kg po dose in the carrageen induced rat paw edema assay. The structures of the dihydropyridyl-1-acetic acid derivatives were expected to have conformational differences relative to the arylacetic acids (NSAIDs).[40]



23

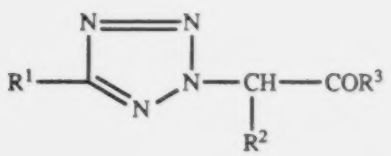


24



25

For example, the 1,4-dihydropyridyl ring is more puckered than a planar phenyl ring system. Although the ene moiety of the 1,4-dihydropyridyl ring system is quasi-planar, there is considerable distortion at the 1,4-dihydropyridyl N-1 and C-4 positons. In addition, the attachment of the acetic acid side chain to a dihydropyridyl sp^3 hybridized nitrogen atom relative to an sp^2 hybridized carbon atom in arylacetic acid NSAIDs, could alter activity and acidity.[40]

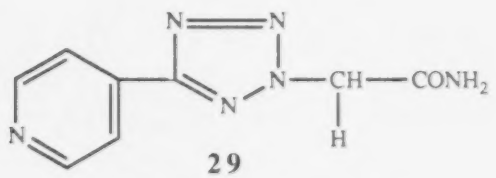


R^1 = 2-pyridyl, 3-pyridyl, 4-pyridyl

R^2 = H, Me

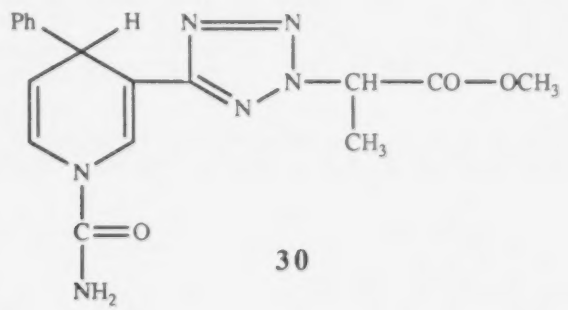
	R^3
26,	OH
27,	OMe
28,	NH_2

A series of 5-(pyridyl)-2*H*-tetrazol-2-acetic acids (**26**, R^3= OH), esters (**27**, R^3= OMe), and amides (**28**, R^3= NH_2) were also synthesised and evaluated as antiinflammatory agents.[41] The most effective antiinflammatory agent in this series was (**29**) which reduced inflammation by 53% at both 3 and 5 hours after a 25 mg/kg po dose. Esterification of NSAIDs has been reported to suppress their gastric ulcerogenic activity, but not to alter antiinflammatory activity appreciably.[42] It is therefore conceivable that the acetamide and acetic acid ester compounds prepared may exhibit a lower degree of gastric ulcerogencity.[41]



29

The C-5 pyridyl-substituent of 5-(pyridyl)-2*H*-tetrazol-2-acetic acids esters, and amides was elaborated to a more lipophilic 1,4-dihydropyridyl ring system in an effort to design NSAIDs that may be devoid of gastric irritation and ulcerogenic effects.[43]



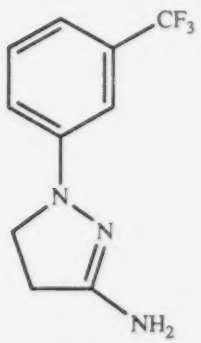
30

Methyl 2-methyl-2-{5-[3-(4-phenyl-1-carbamoyl-1,4-dihydropyridyl)]-2*H*-tetrazol-2-yl}acetate (**30**), was the most effective antiinflammatory agent in the group, reducing inflammation 96% at 5 hours after a 50 mg/kg po dose relative to the reference drug

Ibuprofen (52% inhibition at 5 hours after a 100 mg/kg po dose) in the carrageenan-induced rat paw edema assay.

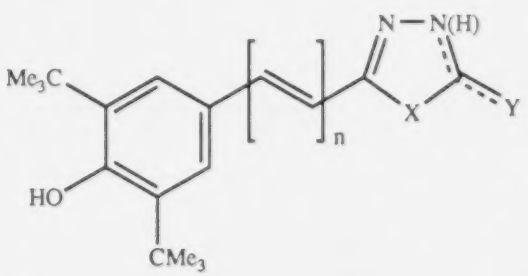
1.1.4.0.0.0. Selective and/or Dual Inhibitors of 5-Lipoxygnase and Cyclooxygenase

It has been postulated that the inhibition of both cyclooxyygenase and 5-lipoxygenase results in a greater antiinflammatory activity than can be achieved by selective cyclooxygenase inhibitors.[44] For example, the phenyl pyrazoline (BW 755C, **31**), which is a dual CO/5-LO inhibitor, exhibits similar antiedema, analgesic and antipyretic activities to Indomethacin, but it is more effective in reducing leukocyte accumulation at therapeutic doses.[45] In addition, BW 755C is thought to limit inflammatory damage and necrosis in a model of foreign body rejection by preventing the accumulation of phagocytic leukocytes.[46]



BW 755C

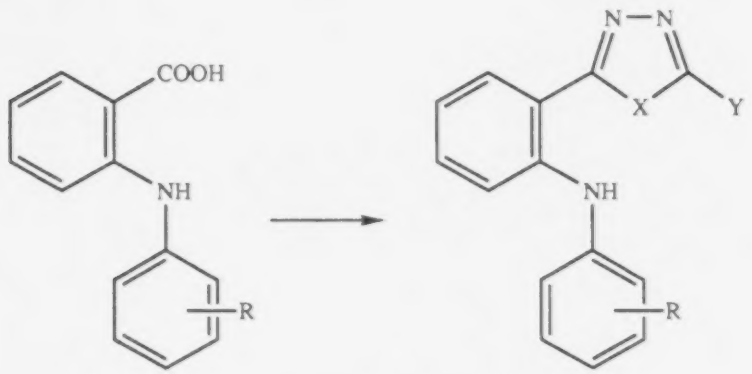
31



32 n = 0, 1; X, Y = O, NH, S

In an attempt to develop a dual CO/5-LO inhibitor, with improved pharmacokinetic properties, Mullicam *et al.*[47] designed and synthesised a series of compounds (**32**) which were found to be potent orally active inhibitors of both 5-LO and CO in rat models of

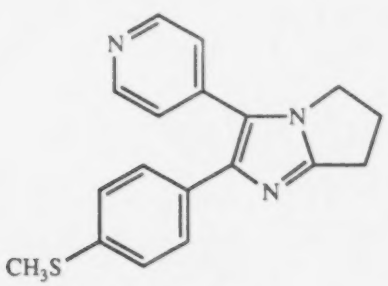
inflammation and were non-ulcerogenic. Replacement of the carboxylic acid group of flufenamic acid (**33a**) and meclofenamic acid (**33b**) with 2-cyanamino-1,3,4-oxadiazoles converted selective cyclooxygenase inhibitiors into dual CO/5-LO inhibitors, while the analogous 2-guanidino compounds were selective 5-LO inhibitiors.[48]



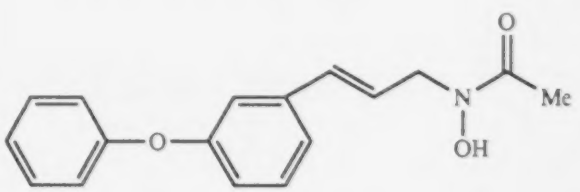
33a, R = 3-CF_3
33b, R = 2,6-Cl_2, 3-Me

X = O, S
Y = NHCN, NHC=(NH)NH_2

Another dual 5-LO/CO inhibitor reported include the pyridyl-substituted 6,7-dihydro-(5*H*)pyrrolo[1,2-a] imidazoles, of which the 4-methylthiophenyl analog (**34**) exhibited effective inhibition of both 5-LO and CO in a variety of *in vitro* and *in vivo* test models.[49]



34



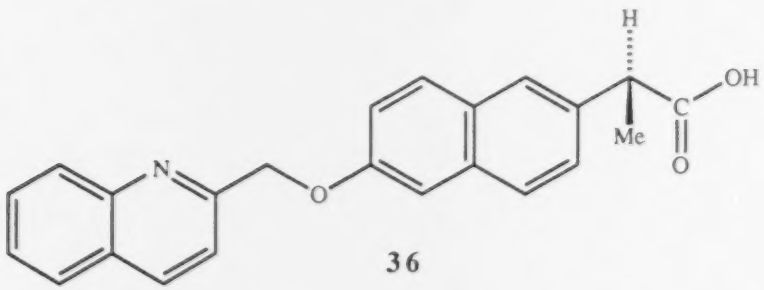
BWA 4C
35

Working on the hypothesis that iron plays a key role in lipoxygenase catalysis,[50] Corey *et al.*[51] synthesised some amide analogs of arachidonic acid in which strong

coordination to iron is possible. It was found that analogs containing a hydroxamic acid moiety were potent and selective inhibitors of 5-LO.

A novel series of acetohydroxamic acid lipoxygenase inhibitors has now been reported[52] of which phenoxycinnamyl hydroxamic acid (BWA 4 **35**) inhibited the synthesis of LTB_4 at lower concentrations than that required to inhibit the synthesis of TXB_2. In contrast BW 755C (**31**) inhibited both enzymes equally.

It has been shown that replacement of the hydroxyl portion of the carboxyl substiuent of Ibuprofen (**3**), a selective CO inhibitor by an NHOH moiety produced the CONHOH analog (**4**) that inhibited both CO and 5-LO.[53] It appeared that 5-LO inhibition was related to decreased ulcerogenicity. (S)-(+)-2-Methyl-6-(2-quinolinylmethoxy)-2-naphthalene-acetic acid (**36**) has also been found to be an orally active 5-LO inhibitor.[54]



36

1.2.0.0.0.0. THE ORIGIN OF INFLAMMATION

The stimulus that precipitates an inflammatory reaction has not yet been fully defined. Speculation revolves around bacterial insult, viral invasion, trauma, and the release of endogeneous hydrolytic enzymes in response to stimuli.[55] However, the events that follow the stimulation have been well characterized and probably involve an initial vasodilation and increased permeability caused by Histamine. This initial reaction is maintained by kinins, notably bradykinin, released from the substrate kininogen by kinin forming enzymes (Kallikreins) activated during the early phase of inflammation.[56] Subsequently, small molecular weight substances, such as prostaglandins, further maintain

the increased vascular permeability and in combination with kinins are responsible for pain.[57,58] It seems probable that these early vascular events are responsible for the four cardinal signs of inflammation described by Celcius (36 BC to 32 AD), that include heat, redness, pain and edema.

It is interesting to note that none of these effects relate to the stimulus or to the chronicity of the inflammatory disease. However, they are accessible to pharmacological intervention. The nonsteroidal antiinflammatory drugs appear to be particulary efficient in limiting these vascular symptoms of acute inflammation.[59,60] Following these early events, there is a wave of polymorphonuclear leukocyte (PMN) migration from the blood vessels to the inflamed tissue.[61] It is assumed that their role is to phagocytize the inflammed tissue, and it is during this process which involves the release of hydrolytic enzymes,[62] that it is possible for the host tissue to be damaged and perhaps to become antigenic.[63] Following this early wave of PMN migration, there is a later phase of monocyte migration.[64] Monocytes, during the process of margination, adherence, diapedesis and chemotactic movement to the site of inflammation, are activated to become macrophages, which are more active phagocytes than PMN.[65] The process by which an acute response is transformed into a chronic event presumably involves the interaction of monocytes, or other accessory cells,[66] with lymphocytes, stimulation of the immune system, and the eventual formation of an antibody.[67] The antigen may be a persistent bacterial cell wall component, viral particle, damaged host tissue, or possibly a combination of these.[68]

The origin of inflammatory reactions can be attributed to a number of mediators which arise in the partial arachidonic acid cascade as illustrated in Figure 1.

Inhibition of PLA_2, CO, 5-LO, and radical species represent four biochemical targets for controlling inflammation. Glucocorticoids inhibit PLA_2, whereas a large number of NSAIDs act primarly via inhibition of endogeneous prostagladin synthesis by blocking the action of the co-enzyme cyclooxygenase.

The Arachidonic Acid Cascade

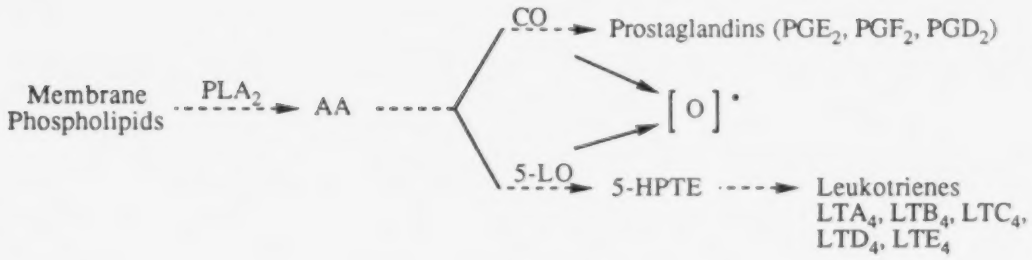


Figure 1. PLA_2 = Phospholipase, AA = Arachidonic acid, CO = Cyclo–oxygenase, 5-LO = 5-Lipoxygenase, 5-HPTE = 5-Hydroperoxy-eicosatetraenoic acid.

1.3.0.0.0.0. STRUCTURE-ACTIVITY RELATIONSHIPS FOR NON-STEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDs)

The present conceptions of the relationship between the chemical structure of nonsteroidal antiinflammatory drugs (NSAIDs) and the respective receptor for antinflammatory action is not completely understood. Shen[69] has proposed a hypothetical model for the receptor using the effective NSAID Indomethacin (**9**), as the model drug as illustrated in Figure 2.

The carboxyl group is bound to a cationic binding site on the receptor, the indole ring system is oriented over a flat area on the receptor surface and the respective supplementary binding sites. The *p*-chlorophenyl moiety is placed in a shallow trough so that the *p*-chlorophenyl moiety is twisted out of the plane of the indole ring system and at an angular position to it. At present, the predominant thought is that the receptor for acidic NSAIDs is represented by cyclooxygenase which catalyses the biosynthesis of prostaglandins. Thus, binding of the acidic NSAIDs to the receptor prevents conversions of the natural substrates

by cyclooxygenase to prostaglandins and the respective endoperoxides. The most important natural substrate appears to be arachidonic acid.[70]

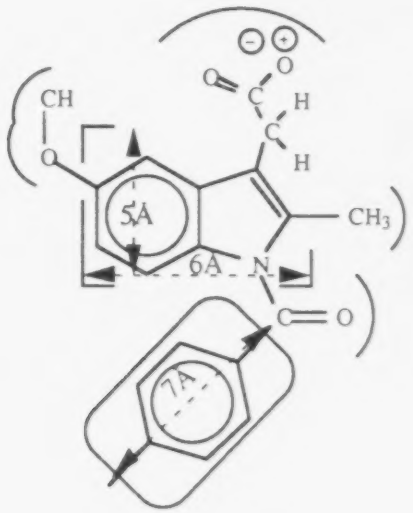


Figure 2. Receptor model based on the chemical structure of Indomethacin.

Gund and Shen[71,72] on the basis of X-ray analysis of NSAIDs and theoretical estimations of the probable conformation of the substrate Arachdonic acid, have improved the conceptions of the chemical relationship between the structure of NSAIDs and the receptor. Accordingly, as illustrated in Figure 3, there is an anionic binding site, and a hydrophobic site or pocket at which the Δ^5 double bond of the arachidonic acid is apparently hydrophobically fixed. In its lower area, the Δ^8, Δ^{11}, and Δ^{14} double bonds of arachidonic acid are bound to these respective electron acceptor regions. The abstraction of a hydrogen atom at the the C-13 position of the arachidonic acid is the initial result of an interaction with the receptor which takes place from above the plane.

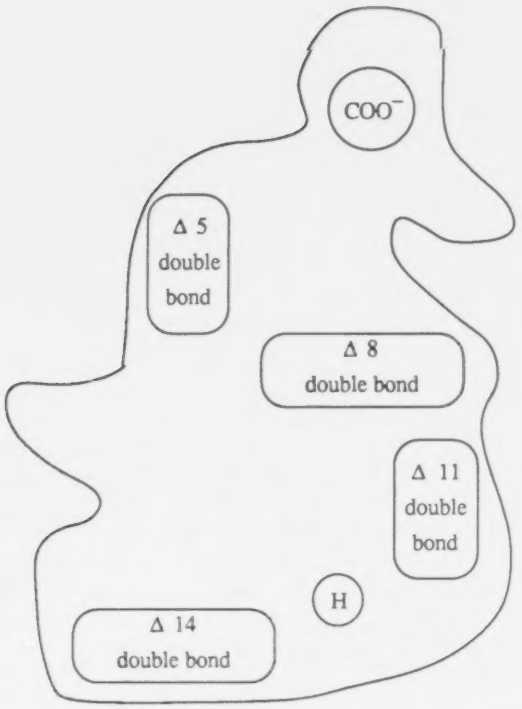


Figure 3. Receptor site for acidic NSAIDs constructed according to the probable conformation of the substrate arachidonic acid (slightly modified).[71,72]

Appleton and Brown[73] were able to identify some common structural features using space-filling models of the peroxy radical as the precursor of the cyclic endoperoxide of arachidonic acid, PGG_2, indole analogs, (S)-2-(3-chloro-4-cyclohexylphenylpropionic acid and other acidic cyclooxygenase inhibitors. The peroxy radical of arachidonic acid (see Figure 4, formula **38**) in its favored conformation immediately prior to its cyclization (formula **39**) is most similar to the structure of (S)-2-(3-chloro-4-cyclohexylphenyl)-propionic acid (**40**) and to that of Indomethacin (**41**), Ketoprofen (**42**), Fenoprofen (**43**), Alclofenac (**44**), Ibuprofen (**45**), and Naproxen (**46**), respectively.

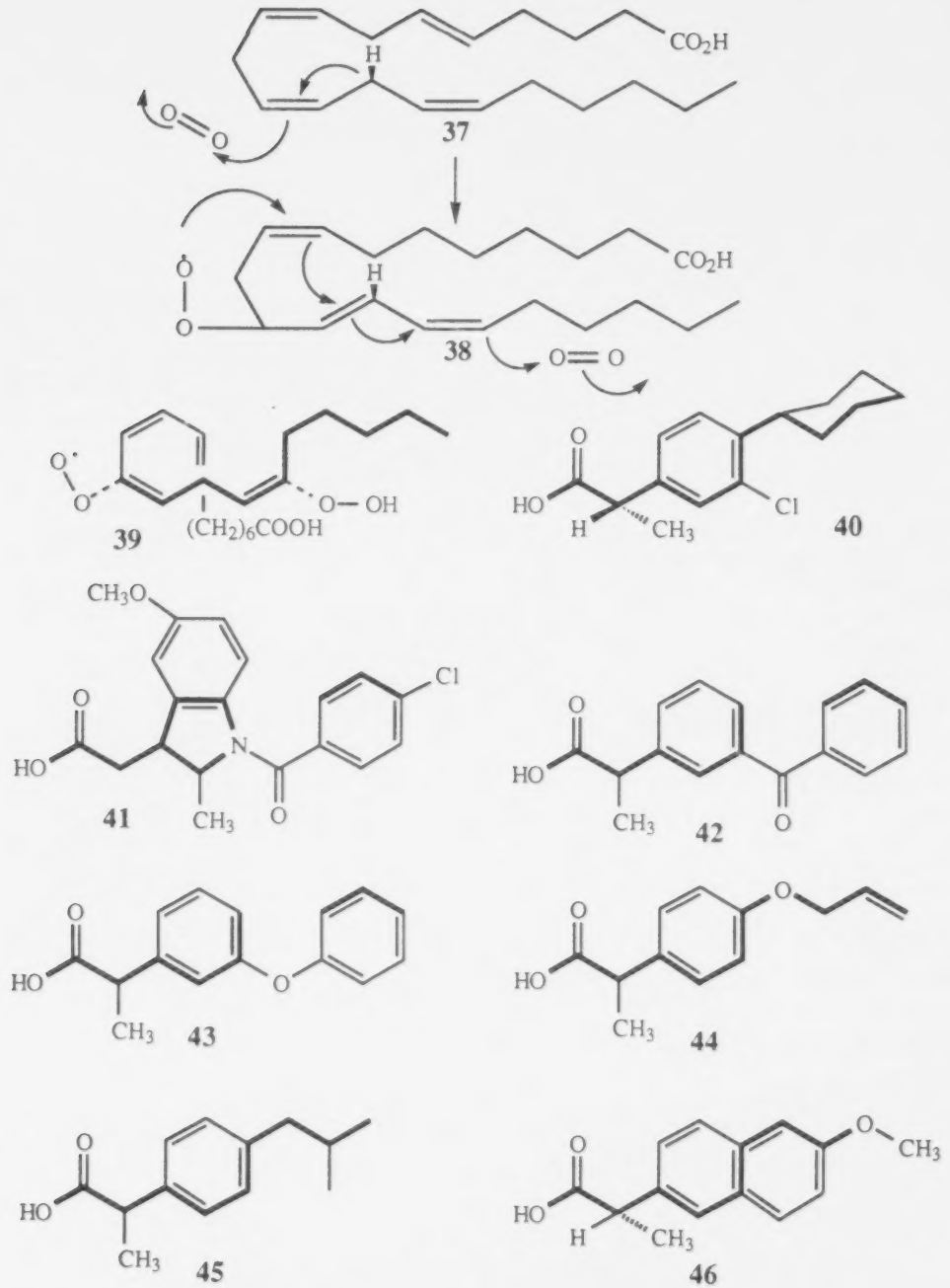


Figure 4: Chemical Structures of the peroxyradical of arachidonic acid (**38**), in its favored conformation (**39**), and of the NSAIDs, (S)-2-(3-chloro-4-cyclohexylphenyl)-propionic acid (**40**), Indomethacin (**41**), Ketoprofen (**42**), Fenoprofen (**43**), Alclofenac (**44**), Ibuprofen (**45**), and Naproxen (**46**), respectively.

The carboxyl group of the NSAID corresponds to, and therefore competes with, the peroxy group in position 11 of the peroxy arachidonic acid. A part of the phenyl ring of **40** could occupy a π-electron acceptor site of the receptor which is related to the π-system of the C_{13}-C_{15} moiety of the physiological substrate. The chlorine atom on the phenyl ring is favorably positioned to disturb the function of the peroxy group at position 15 where oxidation of the fatty acid takes place (Formula **38**). The cyclohexyl ring corresponds to an area of the enzyme which is normally located near a section of the C_{17}-C_{20} chain of the fatty acid. The (S)-methyl substituent lies below the plane of the phenyl ring and would be accomodated by a "groove" in the enzyme which normally accepts the region of C_7 of the physiological substrate. Peterson *et al.*[74,75] have suggested that Indomethacin, Ibuprofen and Tolmetin inhibit cycloxygenase by binding to the cationic binding site which is one of the iron ligands at one side of the heme of the cylooxygenase complex, and by binding to the hydrophobic region of the heme. Accordingly, acidic NSAIDs do not interact with cyclooxygenase itself, but with its heme component.[76,77] In this model, acidic NSAIDs do not interfere with the active site of the cyclooxygenase complex that is represented by the second ligand of iron on the other side of the heme to which iron bound to oxygen interacts with the double bond at C_{11} which is the site of peroxy radical formation of arachidonic acid. Thus, in contrast to arachidonic acid, the acidic NSAIDs are too short and/ or too rigid to wind sterochemically around the protoporphyrin ring in order to reach the second ligand site of the iron. The non-occupation of this second ligand might be the reason for the inability of Indomethacin to inhibit the peroxidase activity of the PG-endoperoxide synthetase enzyme.[74]

These concepts indicate that it is not yet possible to propose a generally valid receptor model and that current conceptions for the fine-structure are not uniform. Hence, the "custom-made" synthesis of NSAIDs with quantitatively and qualitatively better properties is not yet possible. It is possible that additional quantitative structure-activity relationship

(QSAR) data will allow medicinal chemists to design more effective NSAID congeners. In this way, further information may be acquired.

The following structure-activity correlations are generally valid for NSAIDs.[78,79]

1) Three common structural features include the acetic acid side chain, phenyl substituents (X), and a second hydrophobic group (Ar, Alkyl). Figure 5 shown below).

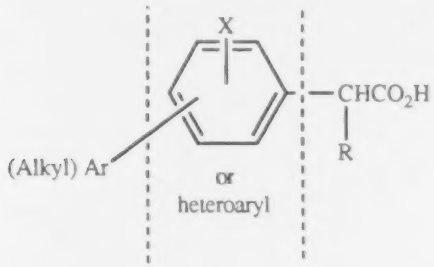


Figure 5. Common structural features of NSAIDs.

2) The carboxyl group, or its equivalent (enolic acid, hydroxamic acid, sulfonamide or tetrazole), is separated by one carbon atom from a flat aromatic nucleus. Increasing this separation to propionic or butyric acid derivatives reduces activity. The latter compounds may undergo conversion to the acetic acid by *in vivo* β-oxidation.

3) An R=Me substituent generally enhances potency. When a chiral carbon atom is present, one enantiomer, usually the (S)-(+)-enantiomer is also the most potent inhibitor of prostaglandin synthetase.

4) One or more large lipophilic groups (Ar, Alkyl) attached to a carbon on the aromatic nucleus increased activity when it is two, three, or four carbon or heteroatoms removed from the point of attachment of the acetic acid side chain.

5) The aromatic and acidic groups may be necessary for efficient binding of the drug to proteins at the site of action, whereas the side chain is required to adjust the overall volume of the molecule and distribution of the drug between hydrophilic and hydrophobic sites.

6) The most effective phenyl (heteroaryl ring) substituents (X) are usually lipophilic electronegative substituents such as F, Cl or CF_3 positioned *meta* to the acid side chain. The substituent (X) may also exert a steric effect to favor a nonplanar arrangement of the second hydrophobic group (Ar, Alkyl).

7) The ester and amide derivatives of aryl and heteroarylacetic acids are also active antiinflammatory agents that are probably hydrolysed *in vivo* to active acids.

1.4.0.0.0.0. SELECTIVITY OF NSAIDs

Recently the medical disciplines have developed a renewed interest in the implications of stereoselectivity with respect to drug action and disposition. The enantiomers of a racemic drug often differ in pharmacodynamic and /or pharmacokinetic properties as a consequence of stereoselective interaction with chiral biological macromolecules.[80] The famous study by Ariens,[81] in which such terms as "isomeric ballast" and "sophisticated nonsense" were used to describe the neglect of stereochemistry for drugs being developed as a mixture of stereoisomers has arguably been the trigger that stimulated an explosive revival in this field.

The justifications for the development of a racemic drug include: additive or synergistic pharmacological activities of both enantiomers, high therapeutic index, negligible/low toxicity of the distomer; chiral inversion occurs to yield a fixed ratio of both enantiomers in

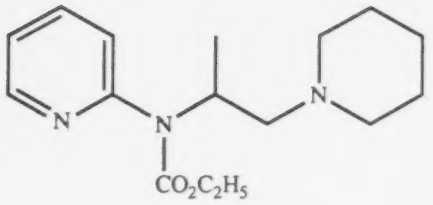
the body, physicochemical properties, novelty of drug product, drug indicated for life-threatening disease, inability/cost-ineffective to resolve active enantiomer on a large scale.[82] On the other hand, the reasons to develop a single enantiomer are: high eudismic ratio of racemate, low therapeutic index, toxicity associated with the distomer, no chiral inversion.[82] Perhaps the issues that should be addressed during the research and development of new candidate drugs with chiral centers should be: similarities/differences between enantiomers (viz.: pharmacology, toxicology, and pharmacokinetics), development of stereospecific assays, chiral inversion, species differences on exposure to enantiomers, therapeutic index of the eutomer, liability of the distomer, difficulty/expense of scale-up synthesis, therapeutic need/novelty and how is the patient best served?

The magnitude of the racemate versus enantiomer question becomes readily apparent with the realisation that the majority of chiral synthetic or semi-synthetic drugs are marketed as racemates.[83] Several chiral 2-arylpropionic acid NSAIDs undergo a relatively unusual metabolic reaction whereby (R)-enantiomers are inverted to the respective (S)-antipodes[84] which has considerable therapeutic significance since antiinflammatory efficacy is mainly, if not exclusively, attributed to the (S)-isomers. The "inactive" (R)-isomer (distomer) may also contribute to the direct GIT irritation and subsequent untoward effects associated with NSAIDs.[85]

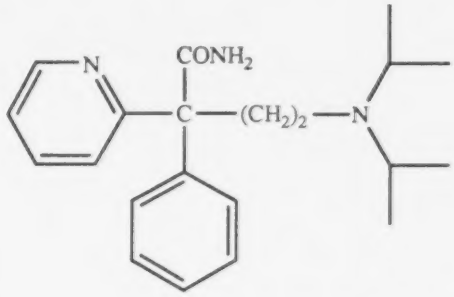
The teratogenic effects of Thalidomide has been ascribed to the (S)-isomer.[86] Ibufenac, which is achiral, is hepatotoxic, whereas (S)-Ibuprofen which is chiral, is not. The question therefore is whether to avoid chiral drugs when possible. No generalizations can be made here but the therapeutically beneficial arguments for enantiomers seem to outweigh those for racemates. The decision should be made on a case by case basis using scientific common sense and keeping in mind that the ultimate goal is to treat the patient with the best available therapeutic drugs.

1.5.0.0.0.0. THE PHARMACOLOGY OF PYRIDINES AND DIHYDRO-PYRIDINES

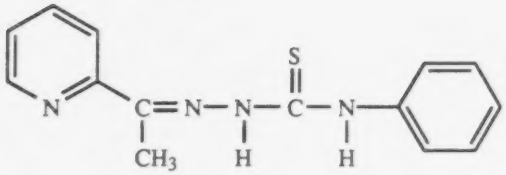
The pyridine ring is one of the most important heterocycles present in pharmaceutical agents.[87] It is present in drugs that exhibit analgesic (**47**)[88], antiarrhythmic (**48**),[89] antimalarial (**49**),[90] antiinflammatory (**50**),[91] hypotensive (**51**)[92] and anticonvulsant (**52**)[93] activities.



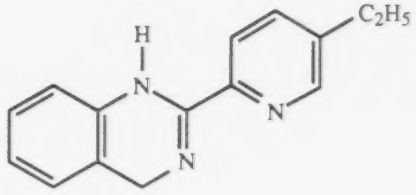
47



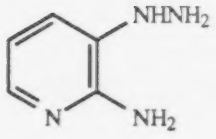
48



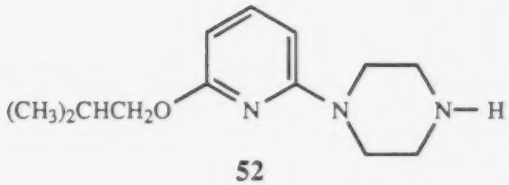
49



50



51



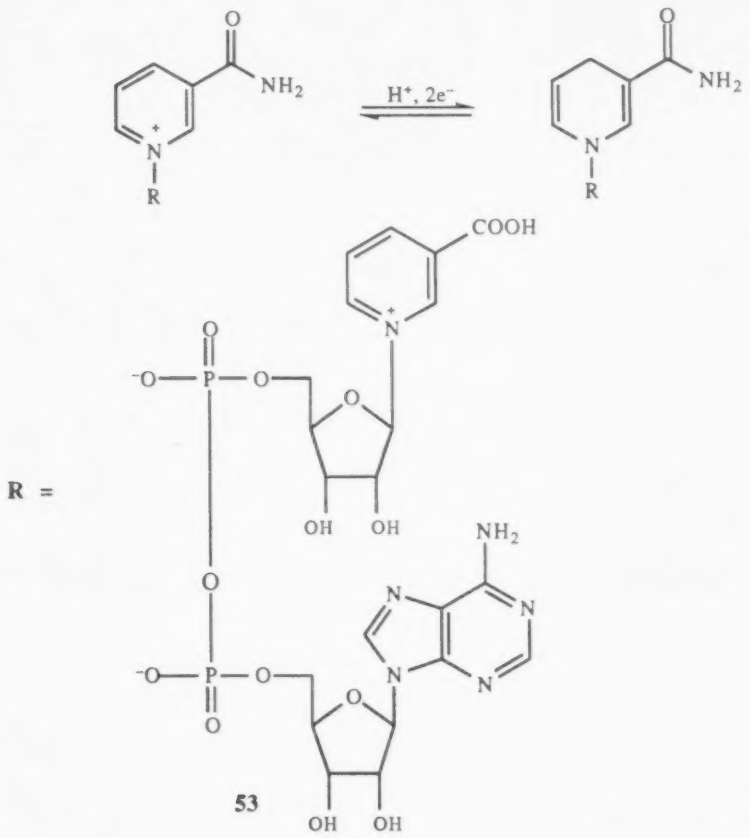
52

Some drugs containing a pyridyl ring have also been developed as vasodilators,[94] while others are used to treat congestive heart failure.[95]

With the discovery in the 1930's that Nicotinamide adenine dinucleotide (NAD^+-NADH) (**44**) was a "hydrogen-transfering coenzyme",[96] dihydropyridines were explored

for possible biochemical and pharmacological properties which led to the development of a number of 1,4-dihydropyridines which possess antiinflammatory,[97] antibacterial,[98] antineoplastic,[99] analgesic,[100] spasmolytic,[101] hepatoprotective,[102-104] antimutagenic,[105] bronchodilating,[106] antithrombolytic,[107,108] antidiabetic,[109,110] and antiepileptic[111] properties. Most extensively studied are the calcium antagonists, whose syntheses[112,113] and properties have been described in a number of reviews.

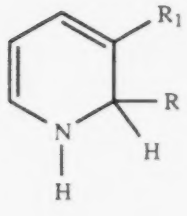
1,4-Dihydropyridines have been used to facilitate drug transfer across the blood-brain barrier.[114-116] For example, the dihydropyridine pyridinium salt redox system has been used to improve the antipyretic activity and distribution of Naproxen and Indomethacin.[117]



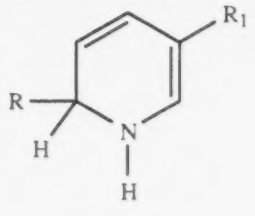
53

1.5.1.0.0.0. The Chemistry of Dihydropyridines

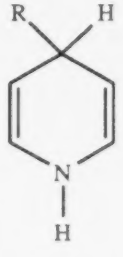
Lyle,[118] Eisner and Kuthan,[119] Kuthan and Kurfurst[120] and Sausins and Duburs[121,122] have published reviews describing the synthesis, structural elucidation, physical and chemical properties of 1,4-dihydropyridines. The most common dihydropyridines are the 1,2- (**54**), 1,6- (**55**), and 1,4- (**56**) analogs of which the 1,4-dihydropyridyl isomers are thermodynamically the most stable.[123]



54



55

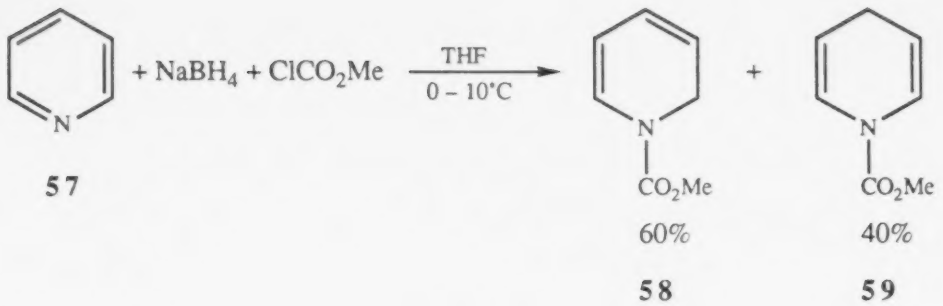


56

Molecular orbital calculations indicate that the nitrogen lone electron pair and the electrons of the two olefinic bonds for 1,4-dihydropyridines are delocalized. Thus, electron-withdrawing substituents at the C-3 and /or C-5 positions therefore enhance stability through substantial delocalisations whilst electron-donating group destabilise the dihydropyridine ring system.[119]

1.5.2.0.0.0. Synthesis of Dihydropyridines

Dihydropyridines and dihydropyridine derivatives, have been employed for the synthesis of nitrogen-containing compounds and natural products.[124] One of the most useful approaches to the intermediates is the reaction, developed by Fowler,[125] that involves the sodium borohydride reduction of N-carbalkoxypyridinium salts formed *in situ* from a pyridine and a chloroformate ester as illustrated in Equation 1.



57 **58** **59**

Equation 1

Sundberg *et al.*[126] have studied substituent effects, and the nature of the reducing agent, on the regioselective reduction of N-carbalkoxypyridinium salts. Abramovitch and co-workers[127] have used London (attractive) forces to explain the *ortho* directing effect observed upon addition of organolithium reagents to 3-alkylpyridines. Knaus and Redda[128] studied the effect of temperature on the sodium borohydride reduction of pyridinium salts. It was found that lowering the temperature of the reaction afforded predominantly the 1,2-dihydropyridine isomer where the ratio of 1,2: 1,4-isomer was 8:1. Reduction of pyridinium salts with sodium dithionite,[129] or a copper hydride complex reagent,[130] yields the 1,4- product.

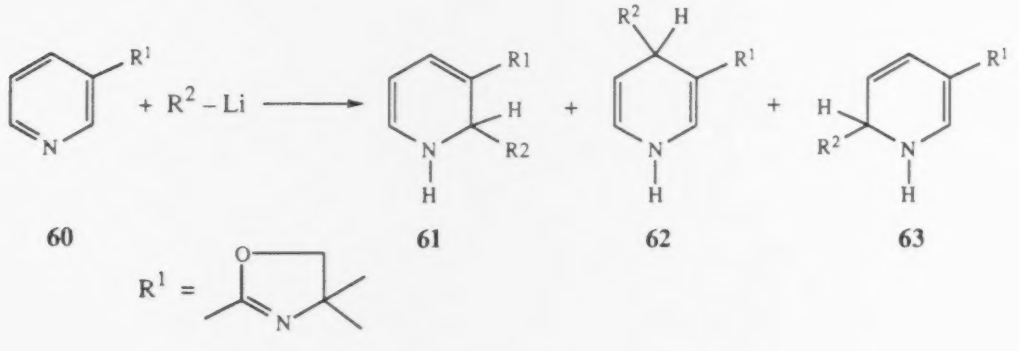
The synthesis of dihydropyridines using organometallic reagents, which is pertinent to this thesis, will be discussed.

1.5.3.0.0.0. Synthesis of Dihydropyridines Using Nucleophilic Organometallic Reagents

Considerable efforts have been directed at the introduction of substituents directly onto the pyridine ring using organometallic reagents.[119,120,124] Several groups such as those of Akiba,[131] Piers,[132] Katritzky,[133] Comins,[134] and Knaus[40,41,43,135] have reported the successful regioselective introduction of allyl or aryl substituents to the 4-position of

pyridine. The regioselectivity of these reactions has been found to be dependent on the nature of the organometallic reagent. Thus, 4-substituted 1,4-dihydropyridines are produced exclusively when organocopper reagents are used[131b,132] whereas Grignard,[136-138] and organocadmium reagents[138] have been reported to yield predominantly 1,2-dihydropyridines.

The effect of solvent, temperature and the nature of the organolithium reagent on the regiochemistry for the nucleophilic addition of organolithium reagents such as phenyl-, *n*-butyl- and methyllithium to 3-(4,4-dimethyloxazolin-2-yl)pyridine (**60**) has been reported by Knaus and Dubey[135] and by Hauck and Giam.[139] It was noted that low temperatures increased the yield of the 1,4-isomer and less polar solvents such as ether gave higher yields of C-2 (**61**) and C-6 (**63**) substituted products. In contrast, reactions performed in tetrahydrofuran provided higher yields of 1,4-dihydropyridine products (**62**) (Equation 2).



Equation 2

Phenyllithium was more regioselective than *n*-butyl- and methyllithium since the former reagent afforded only 1,2- (**61**) and 1,4- (**62**) dihydropyridines, whereas the latter reagent afforded all three isomeric products (**61-63**).

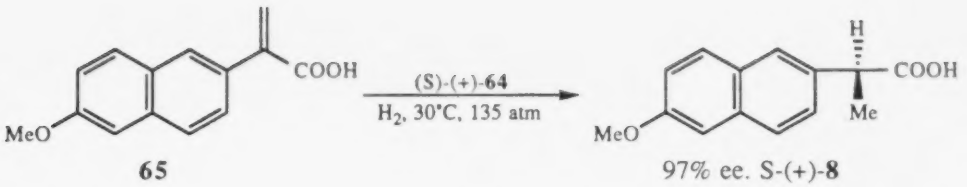
1.5.4.0.0.0. Synthesis of Chiral α-Arylpropanoic Acids

α-Arylpropanoic acids have become an important class of nonsteroidal antiinflammatory agents during the past two decades. The therapeutic efficacy of this class of drugs is now well documented as exemplified by Ibuprofen (**3**), Flubiprofen (**5**), Ketoprofen (**7**) and Naproxen (**8**), just to mention a few examples.

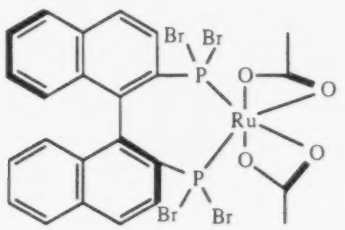
However, in recent years, the use of enantiomerically pure drugs in therapy is becoming mandatory not only to achieve enhanced specificity of drug action but also to avert the possible toxicity and undesirable load on the metabolism by the other enantiomer. This situation applies to the α-arylpropanoic acids due to the higher activity of the (S)-(+)-enantiomer of Ibuprofen and Naproxen.[20] Thus, extensive synthetic efforts have been directed towards the synthesis of chiral NSAIDs.[140] Some representative examples will be discussed.

1.5.5.0.0.0. Hydrogenation of 2-Arylpropenoic Acids

Hydrogenation of olefins using chiral phosphine-rhodium complexes has generated a variety of important products.[141] BINAP-ruthenium dicarboxylate complexes of the type (**64**) have been used to hydrogenate prochiral α,β–unsaturated carboxylic acids to afford chiral saturated acids. Noyori *et al.*,[141c] have demonstrated the efficacy of this reaction for the synthesis of (S)-(+)-Naproxen in 92% chemical yield and an entantiomeric excess of 97% (Equation 3). However the high pressure (135-150 atm) required for this reaction may be a limiting factor.



65 97% ee. S-(+)-**8**

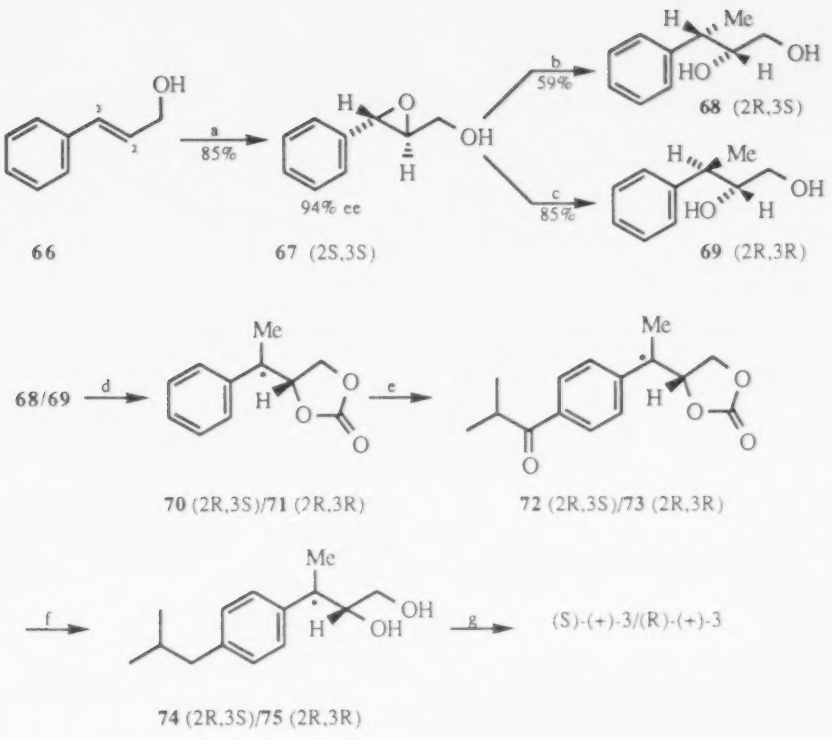


(S)-(+)-**64**

Equation 3

1.5.6.0.0.0. Sharpless Epoxidation

Katsuki and Sharpless[142] found the combination of $Ti(i\text{-}OPr)_4$/(+)-(R,R)-diethyl tartrate (1:1) promoted the enantioselective epoxidation by *t*-BuOOH of many allylic alcohols which was a major advance in asymmetric synthesis. Takana *et al.*[143] have utilized this reaction for the synthesis of both enantiomers (Ibuprofen, **3**) as illustrated in Equation 4. The key step in this entantiodivergent synthesis is the enantiospecific epoxidation of the trans-cinnamyl alcohol (**66**). The subsequent alkylative opening of the oxirane ring using Me_3Al and the organocuprate reagent $Me_2Cu(CN)Li_2$ proceeded with retention and inversion of configuation, respectively.



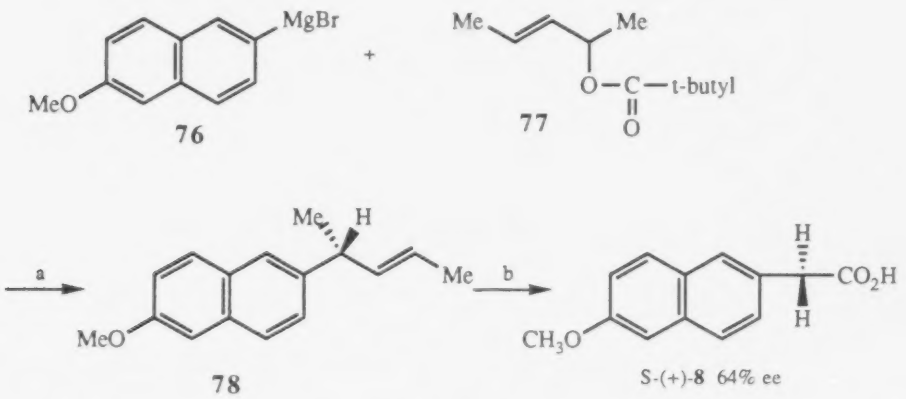
Equation 4

(a) $Ti(i\text{-}OPr)_4$, (+)-DET, TBHP, CH_2Cl_2, -20°C, 3Å molecular sieves; (b) Me_3Al, CH_2Cl_2, -70°C; (c) $Me_2Cu(CN))Li_2$, Et_2O, -50°C; (d) $(EtO)_2CO$, K_2CO_3, 80°C; (e) $Me_2CHCOCl$, $AlCl_3$, CS_2; (f) $NH_2\text{-}NH_2$, H_2O, KOH, $O(CH_2CH_2OH)_2$, -180°C; (g) $RuCl_3 \cdot 3H_2O$, $NaIO_4$, $MeCN/CCl_4/H_2O$ (2:2:3)

1.5.7.0.0.0 Grignard Coupling Reactions

Hiyama and Wakasa[144] reported that the reaction of the pivaloyl ester (**77**) with a variety of arylmagnesium bromides in the presence of the $NiCl_2$[(S,S)-chiraphos] catalyst afforded high chemical yields and optical purity in the C-C bond formation reaction. Thus, reaction of 6-methoxy-2-naphthylmagnesium bromide (**76**) with the pivalate ester (**77**) using $NiCl_2$[(S,S)-chiraphos] as catalyst, afforded (R)-4-(6-methoxy-2-naphthyl)-2-butene

(**78**), which on oxidative cleavage of the double bond produced (S)-(+)- Naproxen (**8**) in a 62% yield with an ee of 64%. (Equation 5.)

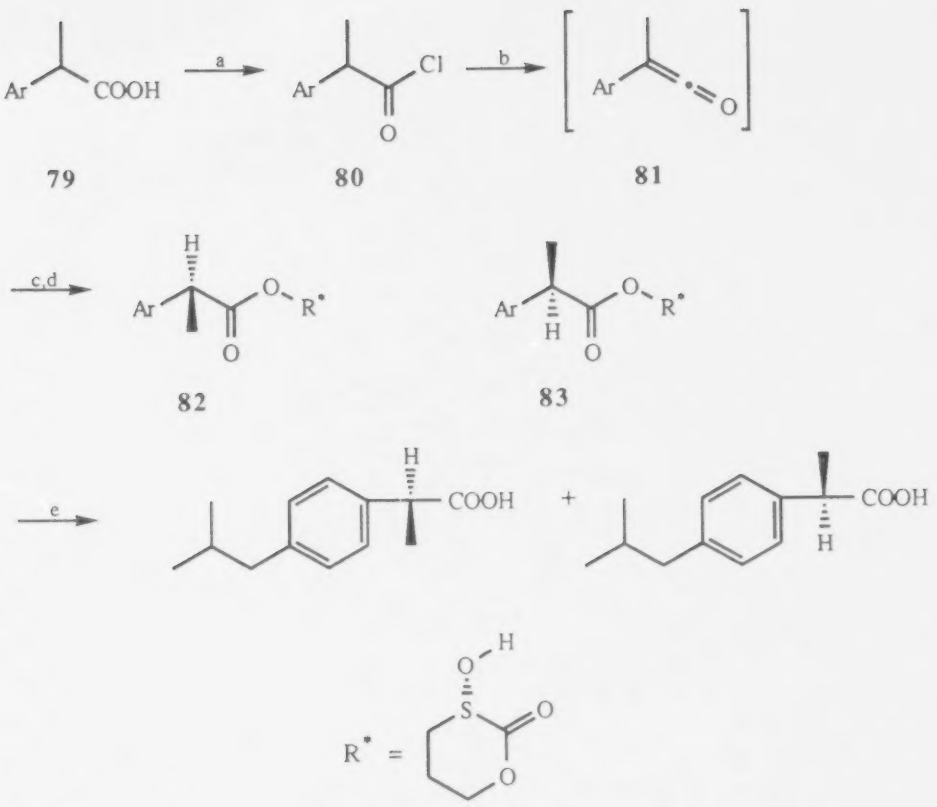


Equation 5

(a) $NiCl_2$[(S,S)-Chiraphos] 0.01 mmol, THF, R.T.; (b) $NaIO_4$, $KMnO_4$.

1.5.8.0.0.0. Enantioselective Protonation

Enantioselective protonation of a suitable derivative is one of the important strategies for the asymmetric transformation of racemic compounds into their optically active form. Larson *et al*,[145] explored the addition of naturally occurring chiral α-hydroxy esters and lactones to the prochiral ketene intermediate derived from a racemic α-arylpropanoic acid which proceeded with a diastereoselectivity of about 99%. It was found that the chiral reagent required a hydroxyl group in close proximity to a hydrogen bonding moiety, such as a carbonyl function, to induce high diastereoselectivity (Equation 6).



Equation 6

Ar = 4-isobutylphenyl; (a) $SOCl_2$, DMF, toluene, 50°C; (b) NEt_3, 25°C; (c) R*OH, toluene, -78°C; (d) CH_3COOH, H_2O, 70°C; (e) CH_3COOH, 2N HCl, 85°C.

2.0.0.0.0.0. OBJECTIVES OF THE RESEARCH

NSAIDs are one of the most frequently prescribed, and therapeutically effective, class of drugs used in the Western world. However undesirable gastrointestinal irritation and bleeding are often associated with the use of NSAIDs. These effects on the gastric and intestinal mucosa are well documented.[146] NSAID gastropathy is a serious iatrogenic problem associated with NSAID therapy which presents a major public health dimension. It is the most common, serious and adverse complication of NSAID therapy identified to date.[147] Armstrong and Blower[148] reported an 80% association of NSAID use with bleeding and occassionally death. Mitchell *et al.*[149] using the U.S. National data bank (ARAMIS), discovered twice the expected incidence of death associated with NSAID induced bleeding. On this basis Fries *et al.*[150] have indicated that at least 2,600 rheumatoid arthritis patients die annually due to NSAID gastropathy complications.

It is not suprising that one of the goals of the pharmaceutical industry was to develop either an NSAID drug that does not damage the gastric mucosa, or a strategy that would prevent or ameliorate damage associated with acute and chronic NSAID administration. A number of strategies have been used in the management of NSAID-induced gastric damage which include enteric tablet coating, incorporation into microspheres, design of pro-drugs and non-acidic derivatives, and the use of drugs that are not soluble at low pH.[151] A number of these approaches have met with a considerable degree of success resulting in direct gastroprotection and enhancement of mucosal defence mechanisms. The development of newer NSAIDs which exhibit considerable clinical efficacy and reduced gastrointestinal adverse effects has been a significant achievement.

There are two major contributing factors responsible for the gastrointestinal ulcerogenicity and hemorrhage resulting from NSAID therapy. These include i) local irritation of the gastric mucosa due to drug acidity and ii) inhibition of Prostagandin E_2 (PGE_2) biosynthesis in the gastric mucosal barrier.[152] Many acidic drugs have a tendency

to accumulate on the stomach wall soon after oral absorption.[153] This process is influenced by the physicochemical properties of the drug. Non-acidic compounds generally have less tendency to accumulate in stomach tissue and they have shown better gastrointestinal tolerance.[154]

The inhibiton of arachidonate cyclooxygenase (CO) is a hallmark feature of virtually all marketed NSAIDs, and this property is believed to play an important role in their therapeutic efficacy.[155] However, the consequences of CO inhibition by NSAIDs result in certain mechanism-based side effects[156,157] including dyspepsia, gastrointestinal ulceration and bleeding, and nephrotoxicity, especially in the elderly population who use them most frequently.[2] The antisecretory amd cytoprotective properties of prostaglandins have been studied intensely[158] and their role in cytoprotection is currently an important area of clinical research. Although inhibition of prostaglandins (via CO inhibition) suppresses inflammation, pain, and fever,[154] PGE_2 also suppresses gastric acid secretion and helps to maintain (cytoprotection) the integrity of the gastric mucosal barrier. Therefore, inhibition of PGE_2 synthesis in the gastric mucosa by NSAIDs removes a natural cytoprotective mechanism resulting in a relative increase in gastric acid production as well as decreased mucosal resistance which is responsible for gastrointestinal (GI) ulcerogenicity and hemmorrhage.[159]

One method to eliminate these adverse GI effects is the design of a class of compounds which are non-acidic and do not accumulate in stomach tissue such as gastric epithelium which is preferably permeable to non-ionized forms of drugs. The design of newer NSAIDs which are tissue specific and inhibit prostaglandin synthesis only at the site of action (joints), but not the GIT, represents a significant challenge in drug design.

A new and novel class of NSAIDs has been discovered viz., 3-benzoyl-4-phenyl-1,4-dihydropyridyl-1-acetic acids, esters and amides which exhibits antiinflammatory activity superior to that of Ibuprofen. The analgesic activity exhibited by these acetic acid, ester and acetamide compounds are also superior to that of Ibuprofen. However, Ibuprofen

induced ulcerogenicity in rat (UD_{50} = 250 mg/kg po) whereas this new class of compounds was completely devoid of any ulcerogenic effects at a dose of 1200 mg/kg po. This class of NSAIDs is novel, since the acetic acid side chain is attached to an sp^3 hybridized nitrogen of a 1,4-dihydropyridyl ring system rather than an sp^2 hybridized carbon atom which is usually the case for other known heteroarylacetic acid NSAID analogs.

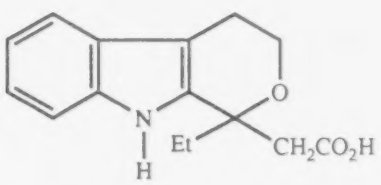
The primary objective of the present research was to design, synthesize and pharmacologically evaluate a novel class of heteroarylacetic acids, esters and acetamides with the hope that they might possess low gastrointestinal ulcerogenicity and be effective in cases where an individual does not respond to other NSAIDs. The scarcity of information on pyridyl and dihydropyridyl analogs of NSAIDs, provided the impetus for this research. In view of the fact that selective biological acitivity may be achieved by the bioisosteric replacement of a phenyl moiety by a pyridyl ring, it was of interest to undertake the design and synthesis, as well as the antiinflammatory and analgesic activity evaluation, of novel pyridine and dihydropyridine analogs of the traditional heteroaryl acetic acid NSAIDs.

3.0.0.0.0.0 RESULTS AND DISCUSSION

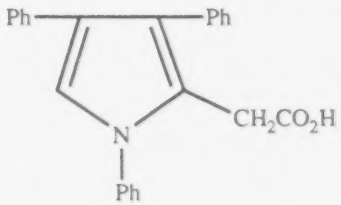
3.1.0.0.0.0. SYNTHESES

3.1.1.0.0.0. Synthesis of 3-Benzoyl-4-substituted-1,4-dihydropyridyl-1-Acetic Acid Esters (90-93), Acetic Acids (97-98) and Acetamides (99)

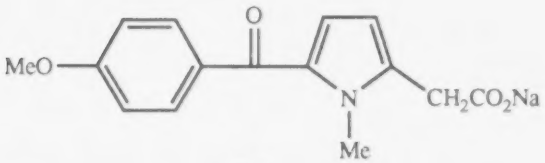
Following the discovery of 4-(2-methylpropyl)phenylacetic acid (Ibufenac, **2**),[8] a large number of arylacetic acids that exhibited analgesic and antiinflammatory activities were synthesized. A number of heteroarylalkanoic acids such as Indomethacin (**9**), Etodolac (**84**), Isofezolac (**85**), and Tolmetin (**86**)[160] have also been developed as anti-inflammatory agents.



84



85



86

The bioisosteric relationship between pyridine and benzene has been discussed. These two ring systems are considered to be classical isosteres.[161] Some pyridylethylphenols have been evaluated as cyclooxygenase and lipooxygenase inhibitors.[162] It was found that the 2- and 3-pyridyl isomers were active, whereas the 4-pyridyl isomer was inactive. Pyridyl analogs of arylethyl phenols have also been shown to exhibit more potent *in vivo*

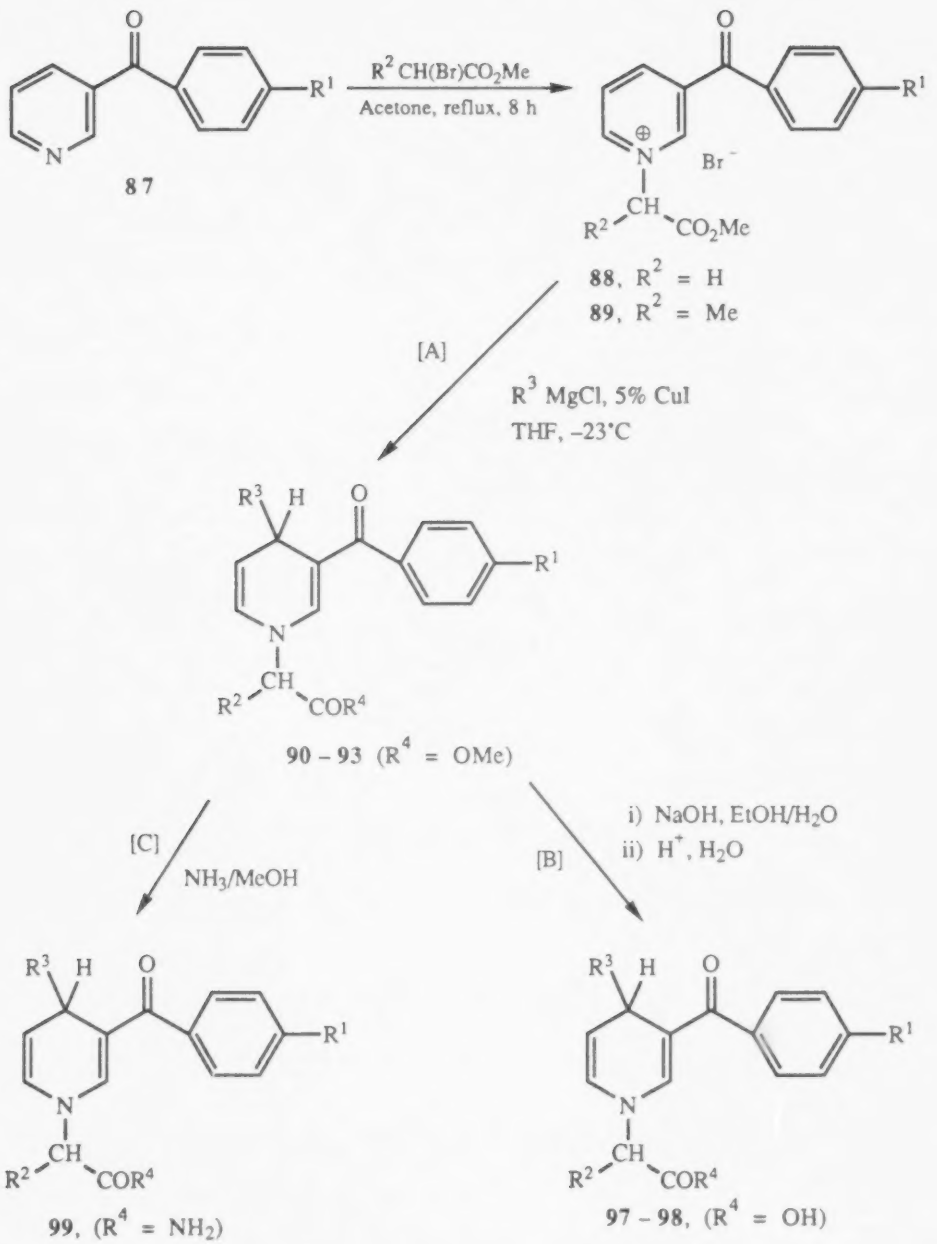
antiinflammatory and higher lipooxygenase inhibitory activity than the corresponding phenyl analogs.[162]

Furthermore, Kumar and Knaus,[40] have described the synthesis and antiinflammatory activity of some N-substituted dihydropyridylacetic acid esters, acetic acids and acetamides.

It was therefore of interest to utilize novel dihydropyridines as synthons for the preparation of N-substituted dihydropyridylacetic acid analogs with the expectation that these analogs might display low gastrointestinal toxicity and be effective in cases where an individual does not respond to non-steroidal antiinflammatory agents. Thus, 3-benzoyl-4-substituted-1,4-dihydropyridyl-1-acetic acid esters (**90**-**93**) were synthesized using the procedure illustrated in Scheme 1 (Method A). It has been proposed that NSAIDs designed to be converted to active forms after absorption from the gastrointestinal tract should, in principle, have reduced GIT side effects[162] since many acidic compounds, including the acidic NSAIDs, have a tendency to accumulate in the stomach wall soon after oral administration.[153] In fact, esterification of NSAIDs has been reported to suppress their gastric ulcerogenicity, but not to alter antiinflammatory activity appreciably.[42]

Thus, the reaction of 3-benzoylpyridine (**87**, R^1 = H) with methyl bromoacetate (R^2 = H) or methyl DL-2-bromopropionate (R^2 = Me) at reflux temperature in dry acetone afforded the corresponding N-substituted-3-benzoylpyridinium salts **88** (R^2 = H) and **89** (R^2 = Me), respectively. The regiospecific copper catalyzed reaction of a Grignard reagent[134] (R^3MgCl) with **88** and **89** afforded the corresponding 3-benzoyl-4-substituted-1,4-dihydropyridine products, **90**-**93**, in 25 to 40% yield.

Product resulting from reaction of the benzoyl carbonyl group with the Grignard reagent was not observed. It has been reported that pyridinium salts are so reactive towards Grignard reagents in the presence of cuprous iodide that addition at the C-4 position of the pyridinium ring is selective in the presence of other reactive functional groups at C-3 such as ketones.[163]



Scheme 1. Synthesis of methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]-acetates and methyl 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates (**90-93**); 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]-acetic acids and 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]-acetic acids (**97, 98**); 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]-acetamides and 2-methyl-2-[1-(3-benzoyl-1,4-substituted-1,4-dihydropyridyl)]acetamides (**99**).

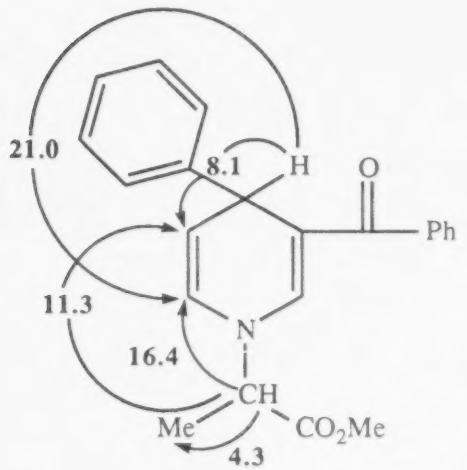
The proton nuclear magnetic resonance (^{1}H NMR) spectral data for compounds **90-93** and **96** indicated that the relative chemical shift positions for the dihydropyridine ring protons (δ) are H-2 > H-6 > H-5 > H-4. These 1,4-dihydropyridyl compounds are very stable due to the electron withdrawing effect of the 3-benzoyl group which is conjugated with the enamine moiety.[119]

1,2- and 1,6-Dihydropyridyl analogs of compounds **90a** and **91** were not obtained when **88** and **89** were treated with Grignard reagent at -23°C in THF in the absence of cuprous iodide. Abramovitch and Singer[164] have reported that reaction of 3-alkyl-1-ethoxypyridinium bromide with Grignard reagents give mainly or exclusively 2-substitution which they attributed to London forces. Also, Lyle *et al.*[138b] have reported that "hard" nucleophiles preferentially attack pyridinium salts at the α-(C-2 and C-6) positions to yield 1,2- and/or 1,6-dihydropyridine products, whereas "soft" nucleophiles add predominantly at the γ-(C-4) position to afford 1,4-dihydropyridines as the major products. The inability to obtain 1,2- and/or 1,6-dihydropyridyl analogs could be due to the greater steric hindrance at the C-2 and C-6 positions of the pyridinium salts **88** and **89** as a consequence of closer proximity to the N-alkyl substituent. Steric hindrance has been reported to be a major factor which prevented the formation of 1,2-dihydropyridine products in the reactions of Grignard reagents with 1-acylpyridinium salts.[134]

Compounds which possessed an R^2 Me substituent exhibited dual resonances in their ^{1}H NMR spectra due to the presence of two chiral centers at C-4 position of the dihydropyridine ring and the chiral methine carbon of the α-methyl acetic acid ester, acetic acid and acetamide moieties. These two chiral centers could give rise to four possible diastereomers SS, SR, RS, and RR. Dual resonances were exhibited by the H-2, H-6, H-5, H-4, and OMe protons approximately in the ratio of 1:1. Compound **91** was separated into an oil **91a** and a solid **91b** by crystallization from ether.

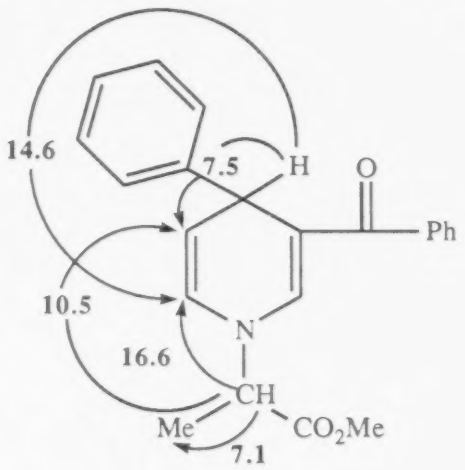
^{1}H NMR nuclear Overhauser enhancement (nOe) studies (Figures 6 and 7) indicated that the magnitude of the nOe effect between the dihydropyridine (DHP) H-4 and its

neighbouring protons is very similar in both compounds **91a** and **91b**. This suggests that the configuration at the C-4 position and the conformation of the DHP ring are similar in both diastereomers (solid and oil).



91a

Figure 6



91b

Figure 7

Nuclear Overhauser enhancement (nOe) spectral data for methyl 2-methyl-2-[1-(4-phenyl-3-benzoyl-1,4-dihydropyridyl)]acetates **91a** and **91b**.

The problems of planarity and non-planarity of the DHP ring has been discussed for many years.[119,165] On the one hand, strong support for a flattened boat-structure is provided by the numerous X-ray structures in the calcium antagonist/agonist series;[165] on the other hand, results of structure investigations of some enzymatic redox co-factors or corresponding model compounds[166-169] imply a planar ring skeleton, although speculations about the boat arrangement exist.[170-172] Hofmann and Cimiraglia,[173] have concluded that the boat conformation of the DHP ring is favoured over the planar ring arrangement but it is highly flexible, with a low barrier between planar and boat-like conformers and that the perpendicular orientation of a phenyl ring in the 4-position of the DHP ring, with respect to the plane of the double bonds (Figure 8), is unequivocally

favoured. Depending on the substituents present, there is some flexibility around this preferred arrangement.

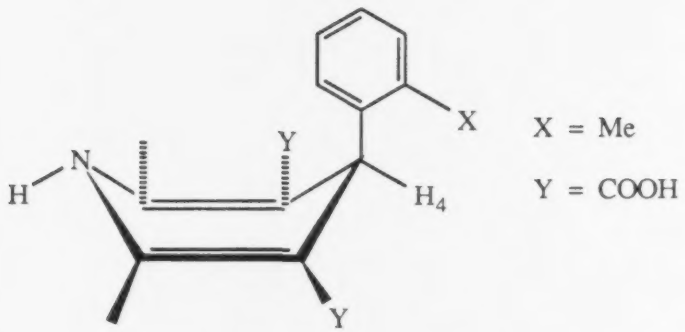
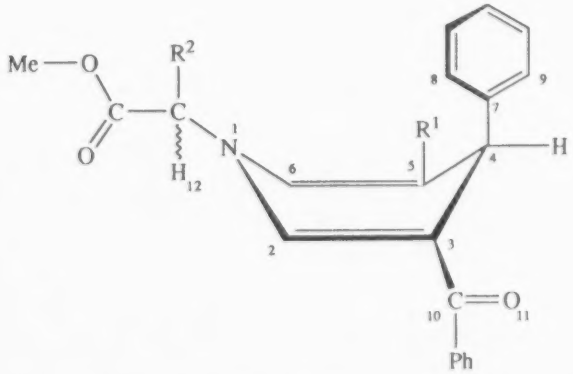


Figure 8. Proposed conformation of a classical calcium antagonist of the 1,4-dihydropyridine type.[173]

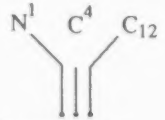
The interatomic distances, bond angles, torsion angles, and local minimum energy determinations for compounds **90**, **91**, **103**, and **104** (Table 1) indicated that these compounds exist in a flat boat conformation with the C-4 phenyl substituent perpendicular or pseudoaxial to the plane of the 1,4-DHP ring. The N(1)-C(4) distance (≅ 2.84 Å) gave a measure of flatness of the boat as compared to the N(1)-(C4) distance (2.66 Å) reported for Nifedipine.[174] Also, the C(2)-C(3)-(C-10)-(O)11 torsion angle indicates that the C=O moiety is synperiplanar to the C(2)-C(3) double bond. The C(2)-C(3)-C(4)-C(7) and C(6)-C(5)-C(4)-C(7) torsion angles, which are generally in the 90-100° range, indicate that the 4-phenyl substituent is perpendicular or pseudoaxial to the plane of the C(2)-(C(3) and C(5)-C(6) olefinic bonds. When the 4-phenyl substituent is pseudoaxial to the boat-shaped 1,4-DHP ring, the configuration at C-4 is the (S)-configuration.

The nOe effects observed for compounds **91a** and **91b** appear to correspond, in part, to the interatomic distances. It is likely that **91a** and **91b** exist as diastereomers since these compounds contain chiral carbons at C-4 of the DHP ring and the α-position of the acetic acid ester moiety. The ^{1}H NMR and ^{13}C NMR spectra for **91a** and **91b** exhibited single resonances. The δ values for H-2, H-4, H-6, and OMe protons in **91a** and **9b** were a little

Table 1. Interatomic distances (Å), bond angles (°), torsion angles (°) and local minimum energy (kcal/mol).[a]



X = NO CHIRAL CENTER



Compound	R^1	R^2
AI90ASSX	H	H
AI90ASRX	H	H
AI#91SSR	H	Me
AI#91SSS	H	Me
AI#91SRR	H	Me
AI#91SRS	H	Me
AI103SXX	PhCO	H
AI104SXR	PhCO	Me
AI104SXS	PhCO	Me

Compound	AI90ASSX	AI90ASRX	AI#91SSR	AI#91SSS	AI#91SRR	AI#91SRS	AI103SXX	AI104SXR	AI104SXS
Interatomic Distances (Å)									
H(2)-H(4)	4.172	4.203	4.160	4.166	4.050	4.034	4.117	4.110	4.111
H(4)-H(5)	2.462	2.448	2.470	2.455	2.679	2.708	—	—	—
H(4)-H(6)	4.115	4.173	4.114	4.100	4.038	4.025	4.118	4.109	4.114
H(5)-H(6)	2.392	2.423	2.389	2.385	2.378	2.378	—	—	—

(Continued)

Compound	AI90ASSX	AI90ASRX	AI#91SSR	AI#91SSS	AI#91SRR	AI#91SRS	AI103SXX	AI104SXR	AI104SXS
Interatomic Distances (Å)									
N(1)-C(4)	2.840	2.732	2.855	2.842	2.862	2.854	2.813	2.799	2.812
N(1)-C(8)	3.627	3.111	3.755	3.635	4.331	4.407	3.580	3.671	3.552
N(1)-C(9)	5.011	4.730	5.041	5.030	5.326	5.338	4.943	5.909	4.961
H(6)-H(12)	ND	ND	2.489	3.597	2.378	3.487	ND	2.485	3.571
H(2)-H(12)	ND	ND	3.773	2.845	3.764	2.967	ND	3.797	2.830
Bond angles (°)									
C(2)-N(1)-C(6)	116.3	113.6	116.1	115.7	116.2	115.4	115.5	116.4	116.2
C(3)-C(4)-C(5)	109.9	107.0	109.2	109.8	110.3	109.7	111.5	111.7	111.9
C(2)-C(3)-C(10)	120.5	123.4	119.0	120.7	120.2	120.0	120.2	119.6	120.7
C(2)-N(1)-C(12)	111.7	111.8	113.0	111.6	112.2	110.8	111.3	113.9	112.4
C(6)-N(1)-C(12)	112.5	111.9	113.7	114.0	110.5	112.4	111.3	113.9	114.9
C(3)-C(4)-C(7)	108.9	110.7	111.5	109.1	110.8	111.7	1079	111.1	107.0
C(5)-C(4)-C(7)	111.0	111.9	110.5	111.8	105.4	104.9	111.8	110.3	111.9

(Continued)

Compound	AI90ASSX	AI90ASRX	AI#91SSR	AI#91SSS	AI#91SRR	AI#91SRS	AI103SXX	AI104SXR	AI104SXS
Torsion angles (°)									
N(1)-C(2)-C(3)-C(4)	0.0	-1.8	-2.0	0.0	-2.7	-2.5	-1.7	-1.3	0.0
N(1)-C(6)-C(5)-C(4)	0.0	2.1	0.0	0.9	1.9	2.3	0.9	0.0	0.0
C(2)-N(1)-C(6)-C(5)	-20.3	-40.0	-20.0	-21.7	-17.8	-22.2	-24.3	-23.4	-21.5
C(3)-C(2)-N(1)-C(6)	20.4	40.2	21.4	21.5	18.4	22.4	24.4	24.1	21.7
C(2)-C(3)-C(4)-C(5)	-18.3	-32.5	-16.9	-18.7	-12.4	-16.1	-20.4	-21.1	-20.0
C(3)-C(4)-C(5)-C(6)	18.5	32.8	18.3	18.7	12.9	16.4	20.6	21.7	20.2
C(2)-C(3)-C(10)-O(11)	-2.1	177.7	-1.7	-2.2	2.0	2.2	-1.4	-2.0	-1.5
C(2)-C(3)-C(4)-C(7)	103.6	89.6	105.4	104.1	-128.7	-132.0	102.7	102.0	102.9
C(6)-C(5)-C(4)-C(7)	-102.0	-88.7	-104.7	-102.5	132.5	136.5	-100.3	-101.8	-99.9
C(5)-C(4)-C(7)-C(8)	41.3	51.5	34.8	44.2	-71.3	-69.4	38.1	29.6	42.1
C(5)-C(4)-C(7)-C(9)	-139.1	-128.5	-145.3	-136.1	110.2	112.0	-142.0	-149.5	-138.4
H(5)-C(5)-C(4)-H(4)	-40.9	-28.0	-42.8	-41.0	72.0	76.0	—	—	—
E min (kcal/mol)	2.9	3.5	3.3	2.1	0.7	1.6	4.8	5.2	4.8

[a]Determined using the Alchemy II minimizer program from Tripos Associates (IBM PC Version).

different (see Table 2). ^{1}H NMR variable temperature studies for a mixture of **91a**:**91b** indicated the absence of rotamers since the dual resonances for H-2, H-4, H-6 and OMe protons did not coalesce.

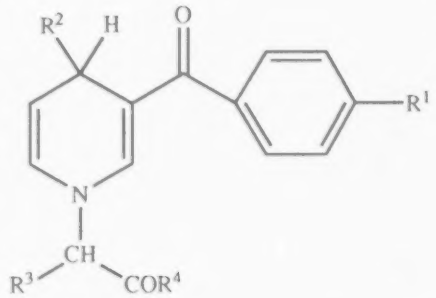
The IR and ^{1}H NMR spectral data for compounds **90-93** and **96**, summarized in Table 2, are consistent with the assigned structures. The physical data are presented in Table 3.

The attachment of the acetic acid side chain to the 1,4-dihydropyridine N-1 sp^3 hybridized nitrogen atom is expected to reduce acidity significantly since the N-substituted acetic acid moiety may be viewed as a glycine (R^2 = H, pK_a = 9.87) or an alanine (R^2 = Me, pK_a of alanine = 9.87) group. These N-substituted acetic acids are expected to be much weaker acids than acetic acid (pK_a = 4.74) or phenylacetic acid (pK_a = 4.25), and should have pK_a's similar to that of phenylalanine (pK_a = 9.24). Therefore, gastric mucosal irritation should be reduced. For example, 5,6-dimethoxyindan-1-acetic acid was found to be a weak acid that exhibited low toxicity and was practically devoid of gastric irritancy at therapeutic doses in antiinflammatory preclinical studies.[175] 2-(4-Chloro-phenylaminoethyl)-4-benzylidene-4,5-dihydro-5-oxo-4-phenylmethylene-1*H*-imidazole-1-acetic acid is also a potent antiinflammatory agent having a low ulcerogenic liability.[176]

The N-substituted 1,4-dihydropyridylacetic acids were synthesized according to Method B as outlined in Scheme 1. Thus, alkaline hydrolysis of **90-93** using aqueous sodium hydroxide (1% w/v) and then acidification with 5 N HCl afforded the acids **97a-98e**. The IR and ^{1}H NMR spectral data for these compounds presented in Table 2 are consistent with their assigned structures. The pK_a of **98a** was determined according to the procedure of Albert and Searjent[177]. The mean pK_a value of **98a** was 9.2, which is in good agreement with the postulated value.

The ulcerogenic liability of 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]-acetic acid (**98a**) was determined according to a modified method reported by Nagai *et al.*[178] Although Ibuprofen was ulcerogenic in rats (UD_{50} = 250 mg/kg po), **98a** was

Table 2. IR and ^1H NMR spectral data for methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates **90a-90c**; methyl 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates **91a-91h**, **92a-92d**, **93**; *ortho*-methoxyphenyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate **96**; 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acids **97a-97c**; 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acids **98a-98e**; 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetamides **99a-99c**; and 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetamides **99d-99j**.



Entry	R^1	R^2	R^3	R^4	IR (neat) cm^{-1}	^1H NMR, $CDCl_3$ (δ)
90a	H	Ph	H	OMe	1721 (COO); 1679 (CO)	7.12-7.5 (m, 10H, phenyl hydrogens), 6.8 (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 5.85 (d, $J_{5,6}$ = 7.7 Hz of d, $J_{2,6}$ = 1.5 Hz, 1H, H-6), 5.1 (d, $J_{5,6}$ = 7.7 Hz of d, $J_{4,5}$ = 4.9 Hz, 1H, H-5), 4.85 (d, $J_{4,5}$ = 4.9 Hz, 1H, H-4), 3.94 (s, 2H, NCH_2), 3.76 (s, 3H, OMe)

(Continued)

Entry	R^1	R^2	R^3	R^4	IR (neat) cm^{-1}	^1H NMR, $CDCl_3$ (δ)
90b	H	4-ClC_6H_4	H	OMe	1745 (COO); 1679 (CO)	7.24-7.5 (m, 9H, phenyl hydrogens), 6.82 (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 5.9 (d, $J_{2,6}$ = 1.5 Hz of d, $J_{5,6}$ = 7.5 Hz, 1H, H-6), 5.08 (d, $J_{5,6}$ = 7.5 Hz of d, $J_{4,5}$ = 4.9 Hz, 1H, H-4), 3.96 (s, 2H, NCH_2), 3.78 (s, 3H, OMe)
90c	H	4-tolyl	H	OMe	1745 (COO); 1679 (CO)	7.06-7.52 (m, 9H, phenyl hydrogens), 6.78 (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 5.86 (d, $J_{2,6}$ = 1.5 Hz of d, $J_{5,6}$ = 7.4 Hz, 1H, H-6), 5.1 (d, $J_{5,6}$ = 7.4 Hz of d, $J_{4,5}$ = 4.9 Hz, 1H, H-5), 4.8 (d, $J_{4,5}$ = 4.9 Hz, 1H, H-4), 3.94 (s, 2H, NCH_2), 3.8 (s, 3H, OMe), 2.28 (s, 3H, tolyl-C$\underline{H}_3$)
91a (oil)	H	Ph	Me	OMe	1745 (COO); 1671 (CO)	7.12-7.5 (m, 10H, phenyl hydrogens), 6.92 (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 5.98 (d, $J_{5,6}$ = 7.7 Hz of d, $J_{2,6}$ = 1.5 Hz, 1H, H-6), 5.06 (d, $J_{5,6}$ = 7.7 Hz of d, $J_{4,5}$ = 4.9 Hz, 1H, H-5), 4.84 (d, $J_{4,5}$ = 4.9 Hz, 1H, H-4), 3.96 (q, J = 7.1 Hz, 1H, C$\underline{H}CH_3$), 3.6 (s, 3H, OMe), 1.36 (d, J = 7.1 Hz, 3H, C$\underline{H}_3$CH).

(Continued)

Entry	R^1	R^2	R^3	R^4	IR (neat) cm^{-1}	^1H and ^{13}C NMR, $CDCl_3$ (δ)
91a (Cont'd) (oil)	H	Ph	Me	OMe	1745 (COO); 1671 (CO)	^{13}C NMR $CDCl_3$ (δ): 194.51 (benzoyl $\underline{C}O$), 171.23 ($\underline{C}O_2Me$), 147.15 (phenyl C-1), 143.23 (C-2), 139.88 (benzoyl C-1), 130.14 (benzoyl C-4), 128.34-126.12 (other phenyl and benzoyl C's), 124.45 (C-6), 113.91 (C-3), 110.46 (C-5), 60.35 ($N\underline{C}HCH_3$), 52.55 ($CO_2\underline{Me}$), 38.0 (C-4), 16.34 ($CH\underline{C}H_3$)
91b (solid)	H	Ph	Me	OMe	1745 (COO); 1671 (CO)	7.1-7.5 (m, 10H, phenyl hydrogens), 6.94 (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 6.04 (d, $J_{2,6}$ = 1.5 Hz of d, $J_{5,6}$ = 7.7 Hz, 1H, H-6), 5.14 (d, $J_{5,6}$ = 7.7 Hz of d, $J_{4,5}$ = 4.9 Hz, 1H, H-5), 4.88 (d, $J_{4,5}$ = 4.9 Hz, 1H, H-4), 4.04 (q, J_{CH,CH_3} = 7.1 Hz, 1H, $C\underline{H}CH_3$), 3.80 (s, 3H, OMe), 1.5 (d, J = 7.1 Hz, 3H, $C\underline{H}_3CH$); ^{13}C NMR $CDCl_3$ (δ): 194.54 (benzoyl $\underline{C}O$), 171.15 ($\underline{C}O_2Me$), 147.12 (phenyl C-1), 143.08 (C-2), 139.75 (benzoyl C-1), 130.12 (benzoyl C-4), 128.40-126.03 (other phenyl and benzoyl C's), 124.7 (C-6), 113.61 (C-3), 110.46 (C-5), 60.19 ($-N\underline{C}HCH_3$), 52.45 ($CO_2\underline{Me}$), 37.96 (C-4), 16.18 ($\underline{C}H_3CH$)

(Continued)

Entry	R^1	R^2	R^3	R^4	IR (neat) cm^{-1}	^1H NMR, $CDCl_3$ (δ)
91c	H	4-ClC_6H_4	Me	OMe	1745 (COO); 1679 (CO)	7.2-7.5 (m, 9H, phenyl hydrogens), 6.98 [6.96] (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 6.0 [6.04] (d, $J_{2,6}$ = 1.5 Hz of d, $J_{5,6}$ = 8.2 Hz, 1H, H-6), 5.06 (d, $J_{5,6}$ = 8.2 Hz of d, $J_{4,5}$ = 4.9 Hz, 1H, H-5), 4.84 [4.82] (d, $J_{4,5}$ = 4.9 Hz, 1H, H-4), 4.0 [4.1] (q, J_{CH,CH_3} = 7.5 Hz, 1H, C<u>H</u>CH_3), 3.74 (two s, 3H total, OMe), 1.44 (d, J_{CH_3CH} = 7.5 Hz, 3H total, C<u>H</u>$_3$CH). Diastereomeric ratio is 3:2. Minor diastereomer is shown in brackets.
91d	H	4-tolyl	Me	OMe	1745 (COO); 1679 (CO)	7.07-7.5 (m, 9H, phenyl hydrogens), 6.96 [6.94] (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 5.94 [5.98] (d, $J_{5,6}$ = 7.7 Hz of d, $J_{2,6}$ = 1.5 Hz, 1H, H-6), 5.08 (d, $J_{5,6}$ = 7.7 Hz of d, $J_{4,5}$ = 5.7 Hz, 1H, H-5), 4.82 [4.8] (d, $J_{4,5}$ = 5.7 Hz, 1H, H-4), 3.96 (q, J_{CH,CH_3} = 7.4 Hz, 1H, C<u>H</u>CH_3), 3.72 (s, 3H total, OMe), 2.28 (s, 3H, tolyl-CH_3), 1.42 (d, J_{CH_3CH} = 7.4 Hz, 3H, C<u>H</u>$_3$CH). Diastereomeric ratio is ≈3:1. Minor diastereomer is shown in brackets.

(Continued)

Entry	R^1	R^2	R^3	R^4	IR (neat) cm^{-1}	^1H NMR, $CDCl_3$ (δ)
91e	H	cyclohexyl	Me	OMe	1753 (COO); 1671 (CO)	7.35-7.65 (m, 5H, phenyl hydrogens), 6.88 (s, 1H, H-2), 6.0 (d, $J_{5,6}$ = 7.6 Hz, 1H, H-6), 4.96 (m, $J_{5,6}$ = 7.6 Hz, 1H, H-5), 3.92 (q, J_{CH,CH_3} = 7.4 Hz, 1H, C<u>H</u>CH_3), 3.76 [3.75] (s, 3H, OMe), 3.7 (m, 1H, H-4), 1.6-1.82 (m, 5H, cyclohexyl H-1, H-2, H-6), 1.46 [1.44] (d, J_{CH_3CH} = 7.4 Hz, 3H, CH_3CH), 1.0-1.3 (m, 6H, cyclohexyl H-3, H-4, H-5). Minor diastereomer is shown in brackets.
91f	H	benzyl	Me	OMe	1745 (COO); 1671 (CO)	7.16-7.6 (m, 10H, phenyl hydrogens), 6.78 [6.72] (d, $J_{2,6}$ = 1.5 Hz, 1H, total, H-2), 5.86 (d, $J_{2,6}$ = 1.5 Hz of d, $J_{5,6}$ = 7.5 Hz, 1H, H-6), 4.9-5.0 (m, 1H, H-5), 4.0-4.12 (m, 1H, H-4), 3.8 (q, J_{CH,CH_3} = 7.4 Hz, 1H, C<u>H</u>CH_3), 3.7 [3.72] (two s, 3H total, OMe), 2.7-3.0 (complex m, 2H, PhCH_2), 1.22 [1.24] (two d, J = 7.4 Hz, 3H total, CHCH_3). Diastereomeric ratio is ≈1:1. Minor diastereomer is shown in brackets.

(Continued)

Entry	R^1	R^2	R^3	R^4	IR (neat) cm^{-1}	^1H NMR, $CDCl_3$ (δ)
91g	H	n-Bu	Me	OMe	1745 (COO); 1679 (CO)	7.3-7.56 (m, 5H, phenyl hydrogens), 6.86 (s, 1H, H-2), 5.94 (d, $J_{5,6}$ = 7.2 Hz, 1H, H-6), 4.98 [5.02] (d, $J_{5,6}$ = 7.2 Hz of d, $J_{4,5}$ = 5.3 Hz, 1H total, H-5), 3.88 (q, J_{CH,CH_3} = 6.8 Hz, 1H, C<u>H</u>CH_3), 3.72 [3.74] (two s, 3H total, OMe), 3.72 (m, 1H, H-4), 1.38 [1.40] (two d, J_{CH_3CH} = 6.8 Hz each, 3H total, C<u>H</u>$_3$CH), 1.2-1.65 (m, 6H, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$$CH_3$). Diastereomeric ratio is ≈2:1. Minor diastereomer is shown in brackets.
91h	H	i-Bu	Me	OMe	1745 (COO); 1679 (CO)	7.34-7.56 (m, 5H, phenyl hydrogens), 6.84 (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 5.9 (d, $J_{2,6}$ = 1.5 Hz of d, $J_{5,6}$ = 7.8 Hz, 1H, H-6), 5.05 (d, $J_{5,6}$ = 7.8 Hz of d, $J_{4,5}$ = 5.5 Hz, 1H, H-5), 3.92 (q, J_{CH,CH_3} = 6.8 Hz, 1H, CH_3C<u>H</u>), 3.74 (s, 3H, OMe), 3.68-3.76 (m, 1H, H-4), 1.56 (m, 1H, -CH_2C<u>H</u>Me_2), 1.35-1.5 (m, 5H, -CHC<u>H</u>$_3$, -C<u>H</u>$_2$$CHMe_2$), 0.88 [0.94] (two d, $_{CH,CH_3}$ = 6.8 Hz, 3H each, -CHC<u>H</u>$_3$). Minor diastereomer is shown in brackets.

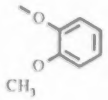
(Continued)

Entry	R^1	R^2	R^3	R^4	IR (neat) cm^{-1}	^1H NMR, $CDCl_3$ (δ)
92a	Cl	Ph	Me	OMe	1745 (COO); 1671 (CO)	7.16-7.46 (m, 9H, phenyl hydrogens), 6.92 [6.90] (two d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 6.0 [5.98] (two d, $J_{2,6}$ = 1.5 Hz of d, $J_{5,6}$ = 8.1 Hz, 1H, H-6), 5.16 (d, $J_{5,6}$ = 8.1 Hz of d, $J_{4,5}$ = 4.8 Hz, 1H, H-5), 4.84 [4.82] (two d, $J_{4,5}$ = 4.8 Hz, 1H, H-4), 4.02 (q, J = 7.5 Hz, 1H, $CH_3C\underline{H}$), 3.78 (s, 3H, OMe), 1.5 (d, J = 7.5 Hz, 3H, $C\underline{H_3}CH$). Diastereomeric ratio ≈1:1. Minor diastereomer is shown in brackets.
92b	Cl	4-ClC_6H_4	Me	OMe	1745 (COO); 1671 (CO)	7.26-7.48 (m, 8H, phenyl hydrogens), 6.94 [6.92] (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 6.02 [6.0] (d, $J_{2,6}$ = 1.5 Hz of d, $J_{5,6}$ = 8.2 Hz, 1H, H-6), 5.08 (d, $J_{5,6}$ = 8.2 Hz of d, $J_{4,5}$ = 4.5 Hz, 1H, H-5), 4.82 [4.80] (d, $J_{4,5}$ = 4.5 Hz, 1H, H-4), 4.02 (q, J = 6.4 Hz, 1H, $C\underline{H}CH_3$), 3.78 (s, 3H, OMe), 1.5 (d, J = 6.4 Hz, 3H, $C\underline{H_3}OH$). Diastereomeric ratio ≈1:1. Minor diastereomer is shown in brackets.
92c	Cl	benzyl	Me	OMe	1753 (COO); 1679 (CO)	7.14-7.56 (m, 9H, phenyl hydrogens), 6.72 [6.74] (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 5.84 (d, $J_{2,6}$ = 2.4 Hz of d, $J_{5,6}$ = 8.6 Hz, 1H, H-6), 4.94 (d, $J_{5,6}$ = 8.6 Hz of d, $J_{4,5}$ = 5.2 Hz, 1H,

(Continued)

Entry	R^1	R^2	R^3	R^4	IR (neat) cm^{-1}	^1H NMR, $CDCl_3$ (δ)
92c (Cont'd)	Cl	benzyl	Me	OMe	1753 (COO); 1679 (CO)	H-5), 4.06 (m, 1H, H-4), 3.76 (q, J = 7.2 Hz, 1H, C<u>H</u>CH_3), 3.68 [3.70] (s, 3H, OMe), 2.84 (m, 2H, Ph$C\underline{H}_2$), 1.24 (d, J = 7.2 Hz, 3H, $C\underline{H}_3CH$). Diastereomeric ratio ≈2:1. Minor diastereomer is shown in brackets.
92d	Cl	cyclohexyl	Me	OMe	1745 (COO); 1679 (CO)	7.54 (d, J = 8.4 Hz, 2H, phenyl H-2, H-6), 7.38 (d, J = 8.4 Hz, 2H, phenyl H-3, H-5), 6.86 (s, 1H, H-2), 6.0 [5.94] (d, $J_{5,6}$ = 8.0 Hz, 1H, H-6), 5.0 [4.98] (d, $J_{5,6}$ = 8.0 Hz of d, $J_{4,5}$ = 5.4 Hz, 1H, H-5), 3.96 (q, J = 7.6 Hz, 1H, C<u>H</u>CH_3), 3.76 (s, 3H, OCH_3), 3.66-3.72 (m, 1H, H-4), 1.56-1.82 (m, 5H, cyclohexyl H-1, H-2, H-6), 1.46 (d, J = 7.6 Hz, 3H, $C\underline{H}_3CH$), 1.0-1.33 (m, 6H, cyclohexyl H-3, H-4, H-5). Diastereomeric ratio ≈1:1. Minor diastereomer is shown in brackets.
93	CH_3	Ph	Me	OMe	1745 (COO); 1679 (CO)	7.10-7.5 (m, 9H, phenyl hydrogens), 6.98 [6.96] (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 5.98 [6.0] (d, $J_{2,6}$ = 1.5 Hz of d, $J_{5,6}$ = 7.5 Hz, 1H, H-6), 5.1 (d, $J_{5,6}$ = 7.5 Hz of d, $J_{4,5}$ = 5.25 Hz, 1H,

(Continued)

Entry	R^1	R^2	R^3	R^4	IR (neat) cm^{-1}	^1H NMR, $CDCl_3$ (δ)
93 (Cont'd)	CH_3	Ph	Me	OMe	1745 (COO); 1679 (CO)	H-5), 4.86 (d, $J_{4,5}$ = 5.2 Hz, 1H, H-4), 4.0 (q, J = 6.75 Hz, 1H, $CH_3C\underline{H}$), 3.76 [3.78] (s, 3H, OCH_3), 2.36 (s, 3H, $PhCH_3$). Diastereomeric ratio ≈3:1. Minor diastereomer is shown in brackets.
96	H	Ph	Me		1769 (COO); 1679 (CO)	6.92-7.60 (m, 15H, phenyl hydrogens, H-2), 6.12 [6.16] (d, $J_{2,6}$ = 1.5 Hz of d, $J_{5,6}$ = 8.1 Hz, 1H, H-6), 5.16 (d, $J_{5,6}$ = 8.1 Hz of d, $J_{4,5}$ = 4.6 Hz, 1H, H-5), 4.88 (d, $J_{4,5}$ = 4.6 Hz, 1H, H-4), 4.26 (q, J = 7.0 Hz, 1H, $CH_3C\underline{H}$), 3.78 (s, 3H, OMe), 1.68 (d, J = 7.0 Hz, 3H, CH_3CH). Diastereomeric ratio is ≈3:2. Minor diastereomer is shown in brackets.
97a	H	Ph	H	OH	3156 (OH); 1802 (COO); 1679 (CO)	DMSO-d_6: 7.12-7.56 (m, 10H, phenyl hydrogens), 7.1 (s, 1H, H-2), 6.12 (d, $J_{5,6}$ = 7.8 Hz, 1H, H-6), 5.0 (d, $J_{5,6}$ = 7.8 Hz of d, $J_{4,5}$ = 4.5 Hz, 1H, H-5), 4.68 (d, $J_{4,5}$ = 4.5 Hz, 1H, H-4), 4.22 (s, 1H, NCH_2)

(Continued)

Entry	R^1	R^2	R^3	R^4	IR (neat) cm^{-1}	^1H NMR, $CDCl_3$ (δ)
97b	H	4-ClC_6H_4	H	OH	3057 (OH); 1819 (COO); 1671 (CO)	DMSO-d_6: 7.30-7.55 (m, 9H, phenyl hydrogens), 7.14 (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 6.12 (d, $J_{2,6}$ = 1.5 Hz of d, $J_{5,6}$ = 7.5 Hz, 1H, H-6), 5.0 (d, $J_{5,6}$ = 7.5 Hz of d, $J_{4,5}$ = 5.1 Hz, 1H, H-5), 1.68 (d, $J_{4,5}$ = 5.1 Hz, 1H, H-4), 4.24 (s, 2H, NCH_2)
97c	H	4-tolyl	H	OH	3057 (OH); 1800 (COO); 1671 (CO)	7.04-7.50 (m, 9H, phenyl hydrogens), 7.0 (s, 1H, H-2), 6.12 (d, $J_{5,6}$ = 7.6 Hz, 1H, H-6), 4.98 (d, $J_{5,6}$ = 7.6 Hz of d, $J_{4,5}$ = 4.8 Hz, 1H, H-5), 44.66 (d, $J_{4,5}$ = 4.8 Hz), 4.16 (s, 2H, NCH_2), 2.2 (s, 3H, tolyl CH_3)
98a	H	Ph	Me	OH	3050 (OH); 1797 (COO); 1671 (CO)	7.12-7.6 (m, 10H, phenyl hydrogens), 7.0 (s, 1H, H-2), 6.75 (broad s, 1H, OH), 5.98 (d, $J_{5,6}$ = 7.8 Hz, 1H, H-6), 5.08 [5.26] (d, $J_{5,6}$ = 7.8 Hz of d, $J_{4,5}$ = 4.6 Hz, 1H, H-5), 4.86 (d, $J_{4,5}$ = 4.6 Hz, 1H, H-4), 3.9 (q, J = 6.4 Hz, 1H, C$\underline{H}$CH_3), 1.48 [1.42] (d, J = 6.4 Hz, 3H, C$\underline{H_3}$CH). Diastereomeric ratio ≈1:1. Minor diastereomer is shown in brackets.

(Continued)

Entry	R^1	R^2	R^3	R^4	IR (neat) cm^{-1}	^1H NMR, $CDCl_3$ (δ)
98b	H	4-ClC_6H_4	Me	OH	3057 (OH); 1802 (COO); 1679 (CO)	7.1-7.7 (m, 9H, phenyl hydrogens), 6.99 [6.96] (two s, 1H total, H-2), 6.7 (bound s, 1H, OH), 6.0 [6.02] (two d, $J_{5,6}$ = 7.05 Hz, 1H total, H-6), 5.05 [5.08] (d, $J_{5,6}$ = 7.05 Hz of d, $J_{4,5}$ = 4.9 Hz, 1H, H-5), 4.8 (d, $J_{4,5}$ = 4.9 Hz, 1H, H-4), 3.95 (q, J = 7.2 Hz, 1H, C<u>H</u>CH_3), 1.48 [1.56] (two d, CH_3CH = 7.2 Hz, 3H total, CH_3CH). Diastereomeric ratio ≈1:1. Minor diastereomer is shown in brackets.
98c	H	cyclohexyl	Me	OH	3057 (OH); 1802 (COO); 1671 (CO)	7.35-7.65 (m, 6H, phenyl hydrogens, H-6), 6.98 [6.92] (two s, 1H total, H-2), 5.62 [5.56] (two d, $J_{5,6}$ = 10.7 Hz of d, $J_{4,5}$ - 4.5 Hz, 1H total, H-5), 4.16 [4.0] (two q, J = 7.14 Hz, 1H, C<u>H</u>CH_3), 3.6-3.25 (m, 1H, H-4), 2.66 (m, 1H, cyclohexyl H-1), 0.98-2.0 (m, 13H, cyclohexyl H-2, H-3, H-4, H-5, H-6, -$CHCH_3$). Diastereomeric ratio of ≈1:1. Minor diastereomer is shown in brackets.
98d	H	benzyl	Me	OH	3080 (OH); 1800 (COO); 1691 (CO)	DMSO-d_6: 7.06-7.62 (m, 10H, phenyl hydrogens), 6.84 (s, 1H, H-2), 5.98 [6.0] (two d, $J_{5,6}$ = 7.7 Hz, 1H, H-6), 4.84 (two overlapping d, $J_{5,6}$ = 7.7 Hz of d, $J_{4,5}$ = 4.9 Hz, 1H

(Continued)

Entry	R^1	R^2	R^3	R^4	IR (neat) cm^{-1}	^1H NMR, $CDCl_3$ (δ)
98d (Cont'd)	H	benzyl	Me	OH	3080 (OH); 1800 (COO); 1691 (CO)	total, H-5), 3.84-4.08 (m, 2H, H-4 and $CH_3C\underline{H}$), 2.76 (m, 2H, $PhC\underline{H}_2$), 1.20 [1.26] (m, 3H, CH_3CH). Diastereomeric ratio of 3:1. Minor diastereomer is shown in brackets.
98e	H	n-Bu	Me	OH	3050 (OH); 1802 (COO); 1679 (CO)	DMSO-d_6: 7.36-7.52 (m, 6H, phenyl hydrogens and H-2), 6.92 [6.12] (two d, $J_{5,6}$ = 7.7 Hz, 1H each, H-6), 4.92 (two overlapping d, $J_{5,6}$ = 7.7 Hz of d, $J_{4,5}$ = 4.9 Hz, 1H total, H-5), 4.28 [4.4] (q, $J_{CH_3,CH}$ = 7 Hz, 1H, $CH_3C\underline{H}$), 3.04 (m, 1H, H-4), 1.12-1.54 (m, 9H, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$, $CHC\underline{H}_3$), 0.93 (t, J = 7.4 Hz, 3H, $C\underline{H}_3CH_2CH_2$). Minor diastereomer is shown in brackets.
98f	H	i-Bu	Me	OH	3080 (OH); 1802 (COO); 1679 (CO)	DMSO-d_6: 7.36-7.52 (m, 5H, phenyl hydrogens), 6.9 [6.92] (two s, 1H total, H-2), 6.08 (d, $J_{5,6}$ = 7.2 Hz, 1H, H-6), 4.98 [5.02] (two d, $J_{5,6}$ = 7.08 Hz of d, $J_{4,5}$ = 4.8 Hz, 1H total, H-5), 4.24 (q, J = 6.9 Hz, 1H, $C\underline{H}CH_3$), 3.58 (m, 1H, H-4), 1.68-1.82 (m, 1H, $CH_2C\underline{H}CH_3)_2$), 1.18-1.44 (m, 5H, $-C\underline{H}_2CH-$, $-CHCH_3$), 0.8-1.0 (m, 6H, $-CH\underline{Me}_2$). Diastereomeric ratio 1:1. Minor diastereomer is shown in brackets.

(Continued)

Entry	R^1	R^2	R^3	R^4	IR (neat) cm^{-1}	^1H NMR, $CDCl_3$ (δ)[a]
99a	H	Ph	H	NH_2	3310, 3810 (NH_2); 1716 (CONH); 1690 (CO)	7.04-7.46 (m, 10H, phenyl hydrogens), 6.8 (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 6.33 and 5.92 (two s, 1H each, NH_2), 5.73 (d, $J_{2,6}$ = 1.5 Hz of d, $J_{5,6}$ = 8.4 Hz, 1H, H-6), 5.08 (d, $J_{5,6}$ = 8.4 Hz of d, $J_{4,5}$ = 4.8 Hz, 1H, H-5), 4.8 (d, $J_{4,5}$ = 4.8 Hz, 1H, H-4), 3.6 (s, 2H, NCH_2)
99b	H	4-ClC_6H_4	H	NH_2	3312, 3180 (NH_2); 1720 (CONH); 1687 (CO)	DMSO-d_6/$CDCl_3$: 7.2-7.5 (m, 10H, phenyl hydrogens, NH), 7.02 (s, 1H, NH, exchanges with deuterium oxide), 6.98 (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 6.0 (d, $J_{5,6}$ = 7.8 Hz of d, $J_{2,6}$ = 1.5 Hz, 1H, H-6), 4.98 (d, $J_{5,6}$ = 7.8 Hz of d, $J_{4,5}$ = 4.8 Hz, 1H, H-5), 4.7 (d, $J_{4,5}$ = 4.8 Hz, 1H, H-4), 3.96 (s, 2H, NCH_2)
99c	H	4-tolyl	H	NH_2	3312, 3180 (NH_2); 1720 (CONH); 1687 (CO)	7.1-7.5 (m, 9H, phenyl hydrogens), 6.82 (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 6.08 and 5.9 (two s, 1H each, NH_2), 5.84 (d, $J_{2,6}$ = 1.5 Hz of d, $J_{5,6}$ = 7.8 Hz, 1H, H-6), 5.14 (d, $J_{5,6}$ = 7.8 Hz of d, $J_{4,5}$ = 5.2 Hz, 1H, H-5), 4.8 (d, $J_{4,5}$ = 5.2 Hz, 1H, H-4), 3.8 (s, 2H, NCH_2), 2.28 (s, 3H, $PhC\underline{H}_3$)

(Continued)

Entry	R^1	R^2	R^3	R^4	IR (neat) cm^{-1}	^1H NMR, $CDCl_3$ (δ)
99d	H	Ph	Me	NH_2	3361, 3301 (NH_2); 1730 (CONH); 1676 (CO)	7.22-7.4 (m, 10H, phenyl hydrogens), 7.02 [7.04] (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 6.14 and 5.75 (two s, 1H each, NH_2, exchanges with deuterium oxide), 6.02 (d, $J_{2,6}$ = 1.5 Hz of d, $J_{5,6}$ = 7.8 Hz, 1H, H-6), 5.18 (d, $J_{5,6}$ = 7.8 Hz of d, $J_{4,5}$ = 4.8 Hz, 1H, H-5), 4.9 (d, $J_{4,5}$ = 4.8 Hz, 1H, H-4), 3.9 (q, J = 7.2 Hz, 1H, $C\underline{H}CH_3$), 1.42 [1.46] (d, J = 7.2 Hz, 3H, CH_3CH). Diastereomeric ratio ≈1:1. Minor diastereomer is shown in brackets.
99e	H	4-ClC_6H_4	Me	NH_2	3312, 3189 (NH_2); 1730 (CONH); 1679 (CO)	7.24-7.56 (m, 9H, phenyl hydrogens), 7.02 (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 6.08 and 5.94 (two s, 1H each, NH_2, exchanges with deuterium oxide), 6.04 (d, $J_{2,6}$ = 1.5 Hz of d, $J_{5,6}$ = 7.6 Hz, 1H, H-6), 5.14 [5.16] (d, $J_{5,6}$ = 7.6 Hz of d, $J_{4,5}$ = 4.8 Hz, 1H, H-5), 4.86 (d, $J_{4,5}$ = 4.8 Hz, 1H, H-4), 3.88 (q, J = 6.3 Hz, 1H, $C\underline{H}CH_3$), 1.46 [1.48] (d, J = 6.3 Hz, 3H, CH_3CH). Diastereomeric ratio ≈1:1. Minor diastereomer is shown in brackets.

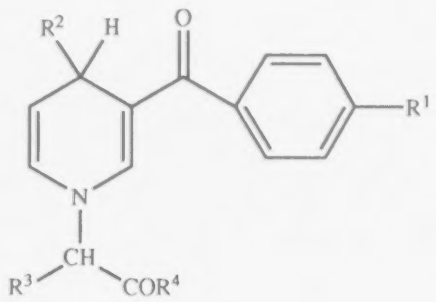
(Continued)

Entry	R^1	R^2	R^3	R^4	IR (neat) cm^{-1}	^1H NMR, $CDCl_3$ (δ)
99f	H	4-tolyl	Me	NH_2	3312, 3180 (NH_2); 1720 (CONH); 1679 (CO)	7.06-7.5 (m, 9H, phenyl hydrogens), 7.0 (s, 1H, H-2), 6.36 and 5.96 (two s, 1H each, NH_2, exchanges with deuterium oxide), 5.92 (d, $J_{5,6}$ = 7.8 Hz, 1H, H-6), 5.1 (d, $J_{5,6}$ = 7.8 Hz of d, $J_{4,5}$ = 4.8 Hz, 1H, H-5), 4.78 (d, $J_{4,5}$ = 4.8 Hz, 1H, H-4), 3.82 (q, J = 6.6 Hz, 1H, C<u>H</u>CH_3), 2.28 (s, 3H, Ph-C<u>H</u>$_3$), 1.36 (d, J = 6.6 Hz, 3H, C<u>H</u>$_3$CH)
99g	H	cyclohexyl	Me	NH_2	3312, 3180 (NH_2); 1720 ($CONH_2$); 1687 (CO)	7.32-7.6 (m, 5H, phenyl hydrogens), 6.88 (s, 1H, H-2), 6.06-6.26 (m, 2H, NH_2, exchanges with deuterium oxide), 6.02 (d, $J_{5,6}$ = 7.6 Hz, 1H, H-6), 5.04 (d, $J_{5,6}$ = 7.6 Hz of d, $J_{4,5}$ = 5.0 Hz, 1H, H-5), 3.84 (q, J = 7.2 Hz, 1H, C<u>H</u>CH_3), 3.72 (d, $J_{4,5}$ = 5.0 Hz, 1H, H-4), 0.8-1.8 (m, 14H, cyclohexyl hydrogens, -CHC<u>H</u>$_3$)
99h	H	benzyl	Me	NH_2	3328, 3180 (NH_2); 1720 (CONH); 1687 (CO)	7.1-7.62 (m, 10H, phenyl hydrogens), 6.66 [6.72] (two d, $J_{2,6}$ - 1.5 Hz, 1H total, H-2), 5.80 [5.83] (two d, $J_{2,6}$ = 1.5 Hz of d, $J_{5,6}$ = 7.2 Hz, 1H total, H-6), 5.34 (s, 1H, NH), 5.0-5.1 (m, 1H, H-5), 4.66 and 4.70 (two s, 1H total, NH), 4.22 (m, 1H, H-4), 3.52 [3.6] (two q, J = 7.5 Hz, 1H total,

(Continued)

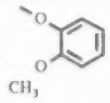
Entry	R^1	R^2	R^3	R^4	IR (neat) cm^{-1}	^1H NMR, $CDCl_3$ (δ)
99h (Cont'd)	H	benzyl	Me	NH_2	3328, 3180 (NH_2); 1720 (CONH); 1687 (CO)	$CHCH_3$), 3.16 (d, J_{gem} = 14.2 Hz of d, J_{vic} = 5.5 Hz, 1H, C<u>H</u>H'-Ph), 2.66 (d, J_{gem} = 14.2 Hz of d, J_{vic} = 2.9 Hz, 1H, CH<u>H</u>-Ph), 1.24 [1.28] (two d, J = 7.5 Hz, 3H total, CH_3CH). Diastereomeric ratio ≈1:1. Minor diastereomer is shown in brackets.
99i	H	n-Bu	Me	NH_2	3328, 3180 (NH_2); 1720 (CONH); 1687 (CO)	7.35-7.8 (m, 5H, phenyl hydrogens), 6.84 (s, 1H, H-2), 6.0 (s, 2H, NH_2, exchanges with deuterium oxide), 5.92 (d, $J_{5,6}$ = 8.6 Hz, 1H, H-6), 5.08 (d, $J_{5,6}$ = 8.6 Hz of d, $J_{4,5}$ = 5.2 Hz, 1H, H-5), 3.84 (q, J = 7.2 Hz, 1H, C<u>H</u>CH_3), 3.74 (m, 1H, H-4), 1.16-1.66 (m, 9H, -$C\underline{H_2}C\underline{H_2}C\underline{H_2}CH_3$, $CHC\underline{H_3}$), 0.93 (t, J = 7.39 Hz, 3H, $C\underline{H_3}CH_2CH_2$)
99j	H	i-Bu	Me	NH_2	3312, 3180 (NH_2); 1720 (CONH); 1687 (CO)	7.36-7.56 (m, 5H, phenyl hydrogens), 6.8 (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 6.05-6.22 (m, 2H, NH_2, exchanges with deuterium oxide), 5.9 (d, $J_{5,6}$ = 7.9 Hz of d, $J_{2,6}$ = 1.5 Hz), 5.16 (d, $J_{5,6}$ = 7.9 Hz of d, $J_{4,5}$ = 4.8 Hz, 1H, H-5), 3.85 (q, J = 7.0 Hz, 1H, C<u>H</u>CH_3), 3.68-3.78 (m, 1H, H-4), 1.7-1.9 (m, 1H, $CH_2C\underline{H}(CH_3)_2$), 1.3-1.54 (m, 5H, -$C\underline{H_2}CHMe_2$, $CHC\underline{H_3}$), 0.90 and 0.96 (two d, J = 6.8 Hz, 6H total, $(CH_3)_2CHCH_2$)•

Table 3. Physical data for methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates **90a-c**, methyl 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates **91-93**; 2-methoxyphenyl-2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate **96**; 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acids **97a-c**; 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acids **98a-e**; 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetamides **99a-c**; and 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetamides **99d-j**.



								Exact Mass	
Entry	R^1	R^2	R^3	R^4	% Yield	m.p. (°C)	Formula	Calcd.	Found
90a	H	Ph	H	OMe	40	oil	$C_{21}H_{19}NO_3$	333.1365	333.1360
90b	H	4-ClC_6H_4	H	OMe	48	oil	$C21H_{18}ClNO_3$	367.0975	367.0975
90c	H	4-tolyl	H	OMe	25	oil	$C_{22}H_{21}NO_3$	347.1521	347.1520
91a	H	Ph	Me	OMe	30	oil	$C_{22}H_{21}NO_3$	347.1521	347.1521

(Continued)

Entry	R^1	R^2	R^3	R^4	% Yield	m.p. (°C)	Formula	Exact Mass	
								Calcd.	Found
91b	H	Ph	Me	OMe	10	140-142	$C_{22}H_{21}NO_3$		a
91c	H	4-ClC_6H_4	Me	OMe	51	oil	$C_{22}H_{20}ClNO_3$	381.1106	381.1104
91d	H	4-tolyl	Me	OMe	28	oil	$C_{23}H_{23}NO_3$	361.1678	361.1685
91e	H	cyclohexyl	Me	OMe	39	oil	$C_{22}H_{27}NO_3$	353.1991	270.1129 (M-cyclohexyl)$^+$
91f	H	benzyl	Me	OMe	28	oil	$C_{23}H_{23}NO_3$	361.1678	361.1658
91g	H	n-Bu	Me	OMe	23	oil	$C_{20}H_{25}NO_3$	327.1834	326.1716 [M-1]$^+$
91h	H	i-Bu	Me	OMe	14	oil	$C_{20}H_{25}NO_3$	327.1834	327.1833
92a	Cl	Ph	Me	OMe	22	oil	$C_{22}H_{20}ClNO_3$	381.1132	381.1131
92b	Cl	4-ClC_6H_4	Me	OMe	27	oil	$C_{22}H_{19}ClNO_3$	415.0739	415.0731
92c	Cl	benzyl	Me	OMe	21	oil	$C_{23}H_{22}ClNO_3$	395.1288	304.0744 [M-benzyl]$^+$
92d	Cl	cyclohexyl	Me	OMe	39	oil	$C_{23}H_{26}ClNO_3$	387.1601	304.0739 [M-cyclohexyl]
93	CH_3	Ph	Me	OMe	50	oil	$C_{23}H_{23}NO_3$	361.1678	361.1674
96	H	Ph	Me		30	oil	$C_{28}H_{25}NO_4$	439.1784	439.1786
97a	H	Ph	H	OH	35	96-98	$C_{20}H_{17}NO_3$		b

(Continued)

Entry	R^1	R^2	R^3	R^4	% Yield	m.p. (°C)	Formula	Exact Mass Calcd.	Exact Mass Found
97b	H	4-ClC_6H_4	H	OH	51	94-96	$C_{20}H_{16}ClNO_3$		b
97c	H	4-tolyl	H	OH	45	100-103	$C_{21}H_{20}NO_3$		b
98a	H	Ph	Me	OH	30	93-95	$C_{21}H_{19}NO_3$		b
98b	H	4-ClC_6H_4	Me	OH	52	98-100	$C_{21}H_{18}ClNO_3$		b
98c	H	cyclohexyl	Me	OH	54	84-86	$C_{21}H_{25}NO_3$		b
98d	H	benzyl	Me	OH	21	83-85	$C_{19}H_{23}NO_3$		b
98e	H	n-Bu	Me	OH	37	68-70	$C_{19}H_{23}NO_3$		b
99a	H	i-Bu	Me	OH	78	89-90	$C_{20}H_{18}N_2O_2$	318.1368	318.1362
99b	H	Ph	H	NH_2	35	80-81	$C_{20}H_{17}ClN_2O_2$	352.0979	352.0972
99c	H	4-ClC_6H_4	H	NH_2	46	85-87	$C_{21}H_{20}N_2O_2$	332.1524	332.1526
99d	H	4-tolyl	H	NH_2	70	70-72	$C_{21}H_{20}N_2O_2$	332.1525	332.1526
99e	H	Ph	Me	NH_2	67	105-107	$C_{21}H_{19}ClN_2O_2$	366.1135	366.1135
99f	H	4-tolyl	Me	NH_2	62	95-96	$C_{22}H_{22}N_2O_2$	346.1681	346.1678
99g	H	cyclohexyl	Me	NH_2	92	90-92	$C_{21}H_{26}N_2O_2$	338.1994	255.1126 $[M\text{-cyclohexyl}]^+$

(Continued)

								Exact Mass	
Entry	R^1	R^2	R^3	R^4	% Yield	m.p. (°C)	Formula	Calcd.	Found
99h	H	benzyl	Me	NH_2	73	85-87	$C_{22}H_{22}N_2O_2$	344.1525	344.1521
99i	H	n-Bu	Me	NH_2	60	70-73	$C_{19}H_{24}N_2O_2$	312.1837	312.1837
99j	H	i-Bu	Me	NH_2	48	78-80	$C_{19}H_{24}N_2O_2$	312.1837	312.1837

[a]Microanalysis: Calcd. (Found); C, 76.06 (76.26); H, 6.09 (6.24); N, 4.03 (3.78).

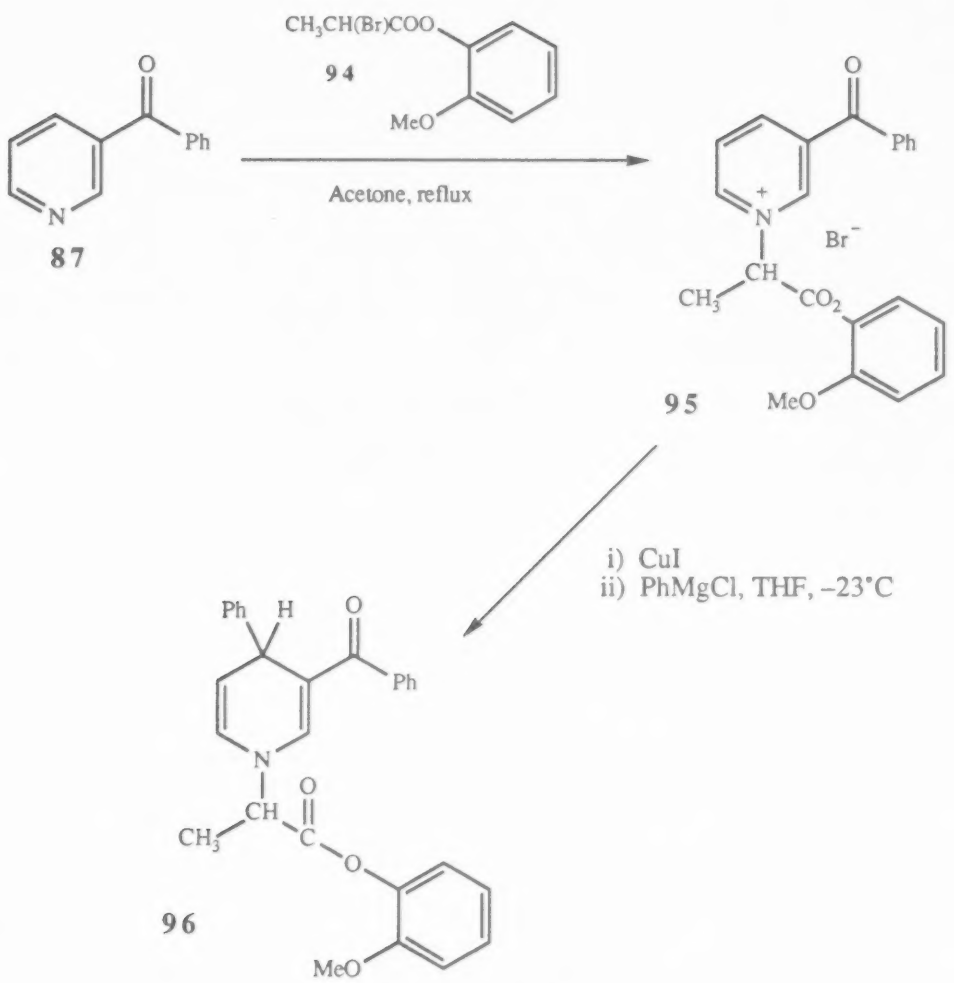
[b]Characterized as the methyl ester prepared by adding a solution of diazomethane to a solution of the acid. The ^1H NMR spectra of the esters prepared in this way were identical to the corresponding ester synthesized.

completely devoid of any ulcerogenic effects at a dose of 1200 mg/kg po for a single oral dose 8 h after administration. A subsequent chronic ulcerogenicity assay using Sprague-Dawley rats showed that **98a** administered at a 600 mg/kg po dose twice a day for 6 days, was completely devoid of any gastric irritation or ulcerogenicity.

The design of prodrugs for NSAIDs represents an important area of drug design and offers great potential as a means of reducing gastric ulcerogenicity. Thus, the synthesis of 3-benzoyl-1,4-dihydropyridylacetamides **99** was undertaken since the acetamides could undergo *in vivo* hydrolysis by ammonolysis to release the acid. In fact, Bundgaard[179] reported that N,N-disubstituted glycolamides were excellent biolabile prodrugs to release the parent active drug following absorption. These prodrugs possess physicochemical properties favourable for peroral absorption as demonstrated in a rabbit study using Naproxen. The 3-benzoyl-1,4-dihydropyridylacetamides were synthesized by ammonolysis of **90-93** using a saturated solution of ammonia in methanol at 25°C for 48 h as described in General Procedure C (Method C, Scheme 1). The IR and ^{1}H NMR spectral data for compound **99** are presented in Table 2, while the physical data are summarized in Table 3.

3.1.2.0.0.0. Synthesis of 2-Methoxyphenyl 2-methyl-2-[1-(4-phenyl-3-benzoyl-1,4-dihydropyridyl)acetate (96)

In the search for non-ulcerongenic non-acidic NSAIDs, Ibuprofen guaiacol ester was synthesized and found to have comparable antiinflammatory potency but greater GIT tolerance than Ibuprofen.[180] This result prompted us to synthesize the guiacol ester **96**. Thus, 3-benzoylpyridine (**87**) was quaternized using 2-methoxyphenyl 2-bromopropionate (**94**) and the resulting 3-benzoylpyridinium salt (**95**) was reduced to the corresponding 1,4-dihydropyridine product **96** according to the General Procedure (Method A) as outlined in Scheme 2. The ^{1}H NMR and IR data presented in Table 2 is consistent with the assigned structure.



Scheme 2. Synthesis of 2-methoxyphenyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (**96**).

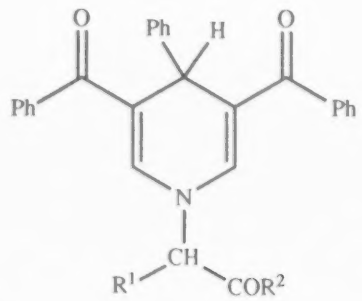
3.1.3.0.0.0. Synthesis of 3,5-Dibenzoyl-4-phenyl-1,4-dihydropyridyl-1-acetic Acid Esters (103 and 104), Acetamides (105 and 106), and Acetic Acids (107 and 108)

There has been an increasing awareness of the need to determine the clinical efficacy of each enantiomer for drugs possessing a chiral center which are used as racemates containing equal quantities of each enantiomer. There are many examples of drugs whose

individual enantiomers have markedly different pharmacological effects,[170] pharmacokinetic and metabolic profiles such as (R)- and (S)-DOPA and (R)- and (S)-penicillamine. A large proportion of the traditional NSAIDs, having an α-methylacetic acid side chain have one chiral center and the S-(+)-enantiomers were generally found to be the most active when the absolute configuration was determined. For example, the S-(+)-enantiomer of 2-(3-phenoxyphenyl)propionic acid (Fenoprofen) or 2-(6-methoxy-2-naphthyl)propionic acid (Naproxen) are respectively 35 and 28 times more active than the corresponding R-(-)-enantiomer.[171,172] Thus, selective synthesis of the physiologically more active enantiomer is highly desirable. It is therefore of interest to synthesize compounds **103-108**. These 3,5-dibenzoyl compounds were synthesized because they have no chiral center at C-4 when R^1 is hydrogen, and one chiral center when R^1 is Me. Acquisition of the two enantiomers of **104**, **106**, and **108** for evaluation of their respective analgesic-antiinflammatory activities would provide useful data correlating chirality with pharmacological efficacy.

Compounds **103** and **104** were synthesized according to General Procedure D, **107** and **108** were synthesized using General Procedure B while the acetamides **105** and **106** were synthesized according to General Procedure C as outlined in Scheme 3. The spectral and physical data are presented in Tables 4 and 5 respectively. The ^1H NMR and ^{13}C NMR spectra showed single resonances. Compound **104** showed two OMe resonances (1:1) when a chiral shift reagent was added and OMe's were deshielded about 0.35 δ.

Table 4. IR and ^1H NMR spectral data for methyl (**103**) and methyl 2-methyl (**104**)-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetates, 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (**105**), 2-methyl 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (**106**) and 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acids (**107** and **108**).

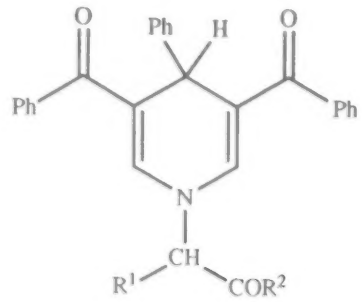


Entry	R^1	R^2	IR (KBr) cm^{-1}	^1H NMR, $CDCl_3$ (δ)
103	H	OMe	1745 (COO); 1622 (CO)	7.1-7.6 (m, 15H, phenyl hydrogens), 6.78 (s, 2H, H-2 and H-6), 5.61 (s, 1H, H-4), 4.1 (s, 2H, NCH_2), 3.84 (s, 3H, OCH_3)
104	Me	OMe	1745 (COO); 1622 (CO)	7.1-7.6 (m, 15H, phenyl hydrogens), 6.92 and 6.89 (two s, 1H each, H-2, H-6), 5.61 (s, 1H, H-4), 4.15 (q, J_{CH,CH_3} = 7.3 Hz, 1H, C<u>H</u>CH_3), 3.81 (s, 3H, OCH_3), 1.54 (d, J_{CH_3CH} = 7.3 Hz, 3H, $C\underline{H}_3CH$). ^{13}C NMR: 194.21 (benzoyl CO), 170.69 (<u>C</u>OOMe), 145.68 (phenyl C-1), 139.55

(Continued)

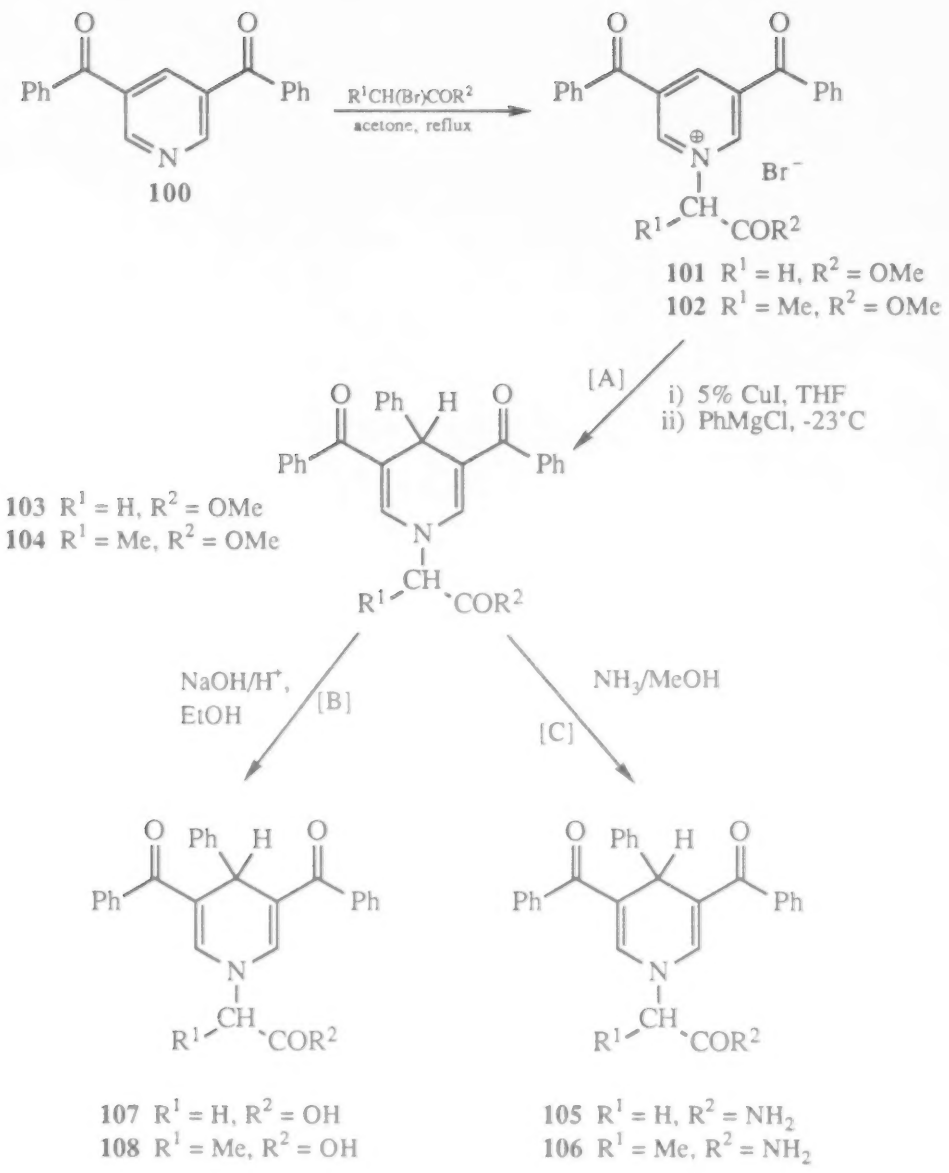
Entry	R^1	R^2	IR (KBr) cm^{-1}	^1H NMR, $CDCl_3$ (δ)
104 (Cont'd.)	Me	OMe	1745 (COO); 1622 (CO)	(C-6), 139.14 (benzoyl C-1), 139.03 (C-2), 130.96 (benzoyl C-4), 130.96-126.36 (other phenyl and benzoyl C's), 119.50 and 119.41 (C-3 and C-5), 60.83 ($N\underline{C}HCH_3$), 52.92 ($\underline{C}O_2CH_3$), 36.98 (C-4), 16.79 ($CH\underline{C}H_3$)
105	H	NH_2	3437, 3331 (NH_2); 1695 (CONH); 1625 (CO)	DMSO-d_6: 7.0-7.5 (m, 15H, phenyl hydrogens), 6.92 (br s, 2H, NH_2), 6.89 (s, 2H, H-2, H-6), 5.39 (s, 1H, H-4), 4.1 (s, 2H, NCH_2)
106	Me	NH_2	3394, 3336 (NH_2); 1690 (CONH); 1622 (CO)	7.01-7.6 (m, 15H, phenyl hydrogens), 6.88 and 6.9 (two s, 1H each, H-2, H-6), 6.34 (br s, 2H, NH_2), 5.56 (s, 1H, H-4), 4.12 (q, $J_{CH.CH_3}$ = 7.0 Hz, 1H, $C\underline{H}CH_3$), 1.5 (d, J_{CH_3CH} = 7.0 Hz, 3H, $C\underline{H}_3CH$)
107	H	OH	3068 (OH); 1720 (COO); 1625 (CO)	$CDCl_3$/DMSO-d_6: 6.7-7.25 (m, 15H, phenyl hydrogens), 6.54 (s, 2H, H-2, H-6), 5.16 (s, 1H, H-4), 3.86 (s, 2H, NCH_2).
108	Me	OH	3016 (OH); 1737 (CO); 1622 (CO)	7.12-7.64 (m, 15H, phenyl hydrogens), 6.92 and 6.95 (two s, 1H each, H-2, H-6), 5.57 (s, 1H, H-4), 4.14 (q, $J_{CH.CH_3}$ = 7.3 Hz, 1H, $CH_3C\underline{H}$), 1.52 (d, J_{CH_3CH} = 7.3 Hz, 3H, $C\underline{H}_3CH$)

Table 5. Physical data for methyl (**103**) and methyl 2-methyl (**104**)-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetates, 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (**105**), 2 methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (**106**) and 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acids (**107** and **108**).



						Microanalysis: Calcd. (Found)		
Entry	R^1	R^2	% Yield	m.p. (°C)	Formula	C	H	N
103	H	OMe	66	160-162	$C_{28}H_{23}NO_4$	76.87 (76.65)	5.36 (5.13)	3.20 (3.28)
104	Me	OMe	32	180-183	$C_{29}H_{25}NO_4$	77.14 (77.18)	5.58 (5.65)	3.10 (3.17)
105	H	NH_2	100	218-220	$C_{27}H_{22}N_2O_3$	76.76 (77.15)	5.25 (5.32)	6.63 (6.72)
106	Me	NH_2	85	231-232	$C_{28}H_{24}N_2O_3$	77.04 (76.66)	5.54 (5.55)	6.42 (6.43)
107	H	OH	72	101-103	$C_{27}H_{21}NO_4$[a]			
108	Me	OH	55	124-125	$C_{28}H_{23}NO_4$[a]			

[a]Characterized as its methyl ester by addition of diazomethane to a solution of the acid. The ^1H NMR spectra of the esters prepared in this way were identical to the corresponding esters synthesized in this way.



Scheme 3. Synthesis of 3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl-1-acetic acid esters (**103** and **104**), acetamides (**105** and **106**) and acetic acids (**107** and **108**).

3.1.4.0.0.0. Ionization Constant Determination

NSAIDs should ideally be weak acids that undergo complete absorption, possess a moderate lipophilicity so a high uptake in inflammed tissue occurs and be devoid of GIT irritation or ulcerogenicity. The pK_a of a compound is defined as the negative logarithm of its dissociation constant K_a, and it is a convenient numerical method to compare the relative acidity or basicity of ionizing compounds in aqueous or miscible solvent-aqueous solutions. The higher the pK_a of a compound, the less acidic it is. Since the acidity of NSAIDs is one of the factors implicated in gastric ulcerogenicity, it was of interest to determine the pK_a of one compound from the 3-benzoyl-4-substituted-1,4-dihydropyridyl acetic acid class of compounds (**97**-**98**).

The pK_a of 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acid (**98a**) was determined using a potentiometric titration method described by Albert and Serjeant.[177] The measurements were carried out in aqueous methanol (H_2O:MeOH = 60:40, v/v) as solvent since compound **98a** was insoluble in water. Newton *et al.*[184] have reported that there was no substantial difference in the precision of pwK_a extrapolated from linear regression plots of psK_a (where pwK_a is the pK_a determined in aqueous medium and psK_a is the pK_a determined in aqueous methanol solutions). All solvents and solutions were properly stored in well-stoppered containers fitted with a Soda-Lime guard tube to exclude carbon dioxide. The pK_a of Ibuprofen was first determined by this procedure to ascertain the precision of the method. Ibuprofen exhibited a pK_a of 5.2 which is the same as the value reported by Davis.[185] From the pH readings and the logarithm of the ratio of the concentrations of acid substrate [HA] and the anion [A^-] during the titration, the pK_a values were calculated according to the Henderson-Hasselbach equation as follows:

$$pK_a = pH + \log[HA] - \log[A^-]$$

Some typical titration data are presented in Table 6. The pK_a values shown in Table 6 are the average of the four values obtained for compound **98a**.

3.1.5.0.0.0. Synthesis of Methyl 2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (111) and Methyl 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (112)

Noyori *et al.*[141c] have reported that ruthenium(II) complexes possessing the 2,2'-bis-(diarylphosphino)-1,1-binaphthyl (BINAP) ligand serve as catalysts for the highly stereoselective hydrogenation of a range of substituted acrylic acids. For instance, the useful antiinflammatory agent (S)-(+)-Naproxen (**8**) was readily synthesized by the asymmetric hydrogenation of 4-(6-methoxy-2-naphthyl)-2-butenoic acid (**78**) as described in Section 1.1.1.9.3.0.

These reports prompted us to synthesize **111** and **112** which could be subjected to stereoselective hydrogenation to prepare two diastereomers which could be separated (from **111**) or a single enantiomer (from **112**) for evaluation as antiinflammatory agents.

Thus, 3-benzoyylpyridine (**87**, R = H) and 3,5-dibenzoylpyridine (**100**, R = PhCO), were quaternized using methyl 2-(bromomethyl)acrylate by refluxing in acetone for 24 h to yield the respective pyridinium salts (**109**, R = H and **110**, R-PhCO). The subsequent reaction of these pyridinium salts with phenylmagnesium chloride in the presence of 5% CuI, according to the General Procedure A, afforded **111** and **112** in 35% and 21% yield respectively.

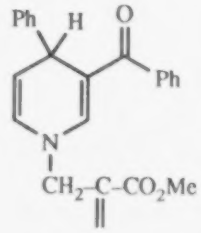
The ^1H NMR and IR spectral data for compounds **111** and **112**, which are consistent with their assigned structures, are presented in Table 7 and the physical data in Table 8. The synthetic route used to prepare **111** and **112** is outlined in Scheme 4.

Table 6. Data for the potentiometric titration of a 0.01 M methanolic solution of 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydro-pyridyl)]acetic acid (**98a**) with a 0.10 M potassium hydroxide solution in water:methanol (60:40, v/v).

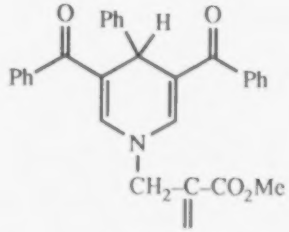
Titrant 0.1 M KOH (mL)	pH	[HA] diminished by tenths	[HA] minus Column 3 = $[A^-]$	$\frac{[HA]}{[A^-]}$	$\log \frac{[HA]}{[A^-]}$	$pK_a^* = pH + \log \frac{[HA]}{[A^-]}$
0	5.92	0.010	0.			
0.5	8.45	0.009	0.001	9/1	0.95	9.40
1.0	8.58	0.008	0.002	8/2	0.60	9.18
1.5	8.79	0.007	0.003	7/3	0.37	9.16
2.0	8.96	0.006	0.004	6/4	0.18	9.14
2.5	9.17	0.005	0.005	5/5	0	9.17
3.0	9.35	0.004	0.006	4/6	-0.18	9.17
3.5	9.56	0.003	0.007	3/7	-0.37	9.19
4.0	9.74	0.002	0.008	2/8	-0.60	9.14
4.5	9.95	0.001	0.009	1/9	-0.95	9.00
5.0	10.3	0	0.010			

*Result: $pK_a = 9.17 \pm 0.01$.

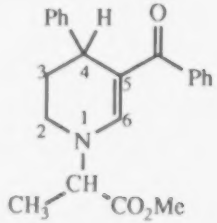
Table 7. IR and ^1H NMR data for methyl 2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**111**), methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**112**), and methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydropyridyl)]acetate (**113**).



111



112



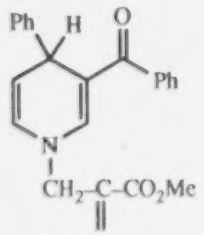
113

Entry	IR (neat) cm^{-1}	^1H NMR ($CDCl_3$) δ
111	1745 (COO); 1679 (CO)	7.1-7.5 (m, 10H, phenyl hydrogens), 6.96 (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 6.38 (s, 1H, =CHH'), 5.94 (d, $J_{2,6}$ = 1.5 Hz of d, $J_{5,6}$ = 7.5 Hz, 1H, H-6), 5.78 (s, 1H, =CHH'), 5.12 (d, $J_{5,6}$ = 7.5 Hz of d, $J_{4,5}$ = 4.6 Hz, 1H, H-5), 4.9 (d, $J_{4,5}$ = 4.6 Hz, 1H, H-4), 4.08 (s, 2H, NCH_2), 3.8 (s, 3H, OCH_3)
112	1745 (COO); 1679 (CO)	7.1-7.7 (m, 15H, phenyl hydrogens), 6.88 (s, 2H, H-2, H-6), 6.38 (s, 1H, =CHH'), 5.74 (s, 1H, =CHH'), 5.62 (s, 1H, H-4), 4.12 (s, 2H, NCH_2), 3.8 (s, 3H, OCH_3)

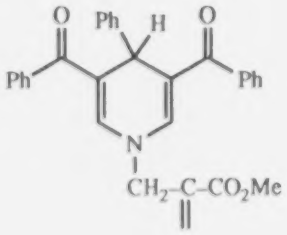
(Continued)

Entry	IR (neat) cm^{-1}	^1H NMR ($CDCl_3$) δ
113	1745 (COO); 1679 (CO)	7.24-7.65 (m, 11H, 9 phenyl hydrogens, H-2, H-6), 7.18 (m, 1H, p-phenyl H), 4.38 (dd, $J_{3,4}$ = 5.0 Hz, 1H, H-4), 3.88-4.02 (overlapping quartets, J_{CH,CH_3} = 7.2 Hz, 1H, C<u>H</u>CH_3), 3.74 [3.76] (s, 3H total, OCH_3), 2.9-3.18 (m, 2H, H-2), 1.9-2.15 (m, 2H, H-3), 1.44 [1.42] (two d, J_{CH_3CH} = 7.2 Hz, 3H total, C<u>H</u>$_3$CH)
		Diastereomeric ratio 1:1

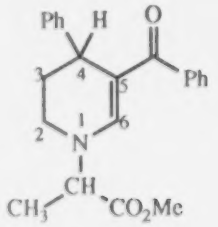
Table 8. Physical data for methyl 2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**111**), methyl 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**112**), and methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydropyridyl)]acetate (**113**).



111

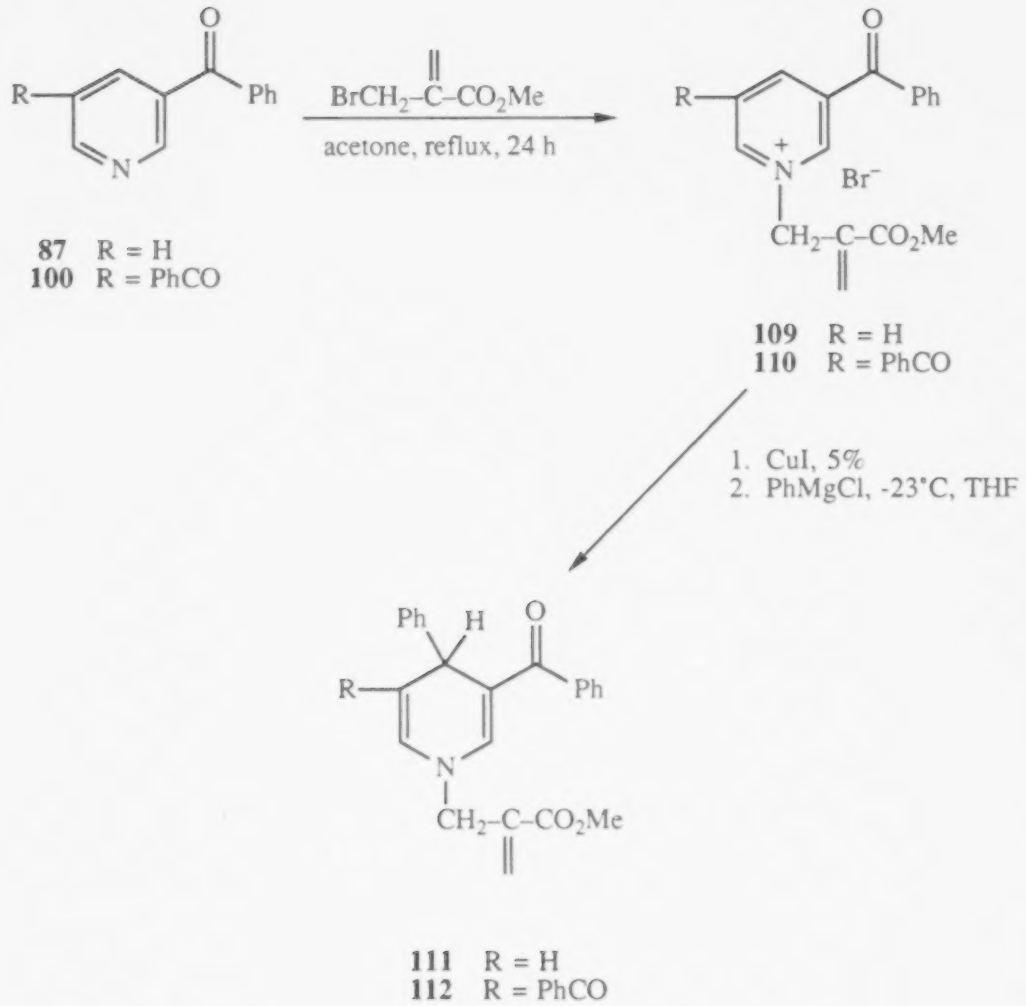


112



113

				Microanalysis: Calcd. (Found)		
Entry	Yield, %	m.p., °C	Formula	C	H	N
111	35	oil	$C_{23}H_{21}NO_3 \cdot 3/4H_2O$	74.01 (73.87)	5.61 (5.58)	3.76 (3.92)
112	21	oil	$C_{30}H_{25}NO_4 \cdot H_2O$	74.84 (75.18)	5.20 (5.15)	2.91 (3.01)
113	47	oil	$C_{23}H_{23}NO_3 \cdot 1/2H_2O$	73.65 (73.30)	6.42 (6.36)	3.91 (3.94)



87 R = H
100 R = PhCO

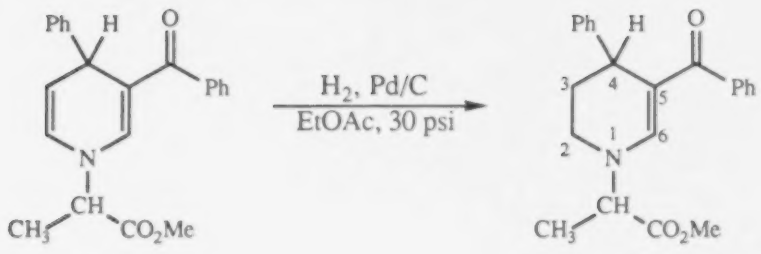
109 R = H
110 R = PhCO

111 R = H
112 R = PhCO

Scheme 4. Synthetic route for the preparation of **111** and **112**.

3.1.6.0.0.0. Synthesis of Methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydropyridyl)]acetate (113)

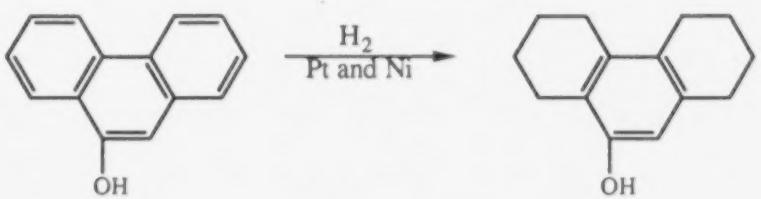
Compound **113** was synthesized in order to investigate the effect of the C5-C6 double bond present in **91** on antiinflammatory and analgesic activity. Thus, compound **91b** was subjected to hydrogenation with hydrogen gas at 30 psi in the presence of 10% palladium-on-charcoal in ethyl acetate at 25°C to afford the corresponding tetrahydropyridine **113** as



91b **113**

Scheme 5. Synthesis of methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydropyridyl)]acetate (**113**).

outlined in Scheme 5. The C2-C3 double bond of **91** was not reduced, presumably due to steric factors. As mentioned earlier, compound **91** exists in a flat boat conformation with a C-4 axial phenyl group. Therefore, hydrogen addition occurs preferentially at the less-hindered C5-C6 double bond of **91b**. The effect of steric factors on hydrogenation of C-C double bonds has been studied.[186] Linstead and co-workers,[186] based on studies involving the hydrogenation of phenanthrene and diphenic acid derivatives, concluded that the less-hindered side of an unsaturated molecule is adsorbed on the catalyst surface and this has led to the generalization that catalytic hydrogenation of a multiple bond results in *cis* addition of two hydrogen atoms from the less-hindered site. For example, when 9-phenanthrol **114** was hydrogenated over platinum in acetic acid, the octahydro-9-phenanthrol **115**, was obtained indicating reduction of the non-hindered double bonds (Scheme 6).[186]

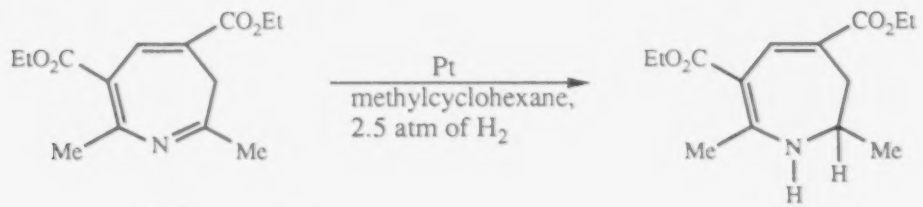


114 **115**

Scheme 6. Catalytic hydrogenation of 9-phenanthrol (**114**)

The IR and ^1H NMR spectral data, which are consistent with the structure for compound **113**, are presented in Table 7 and the physical data in Table 8. The ^1H NMR spectrum does not display resonances in the δ 5-6 region indicating the absence of the C5-C6 olefinic bond of **91b**. Also, the IR spectrum shows the absence of an isolated olefinic bond in the 1650 cm^{-1} region.

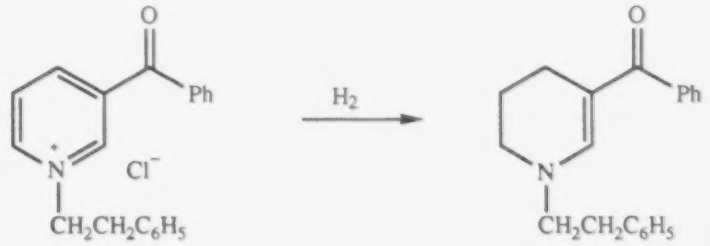
The failure of the N–C=C–C=O moiety to undergo hydrogenation is further illustrated by partial hydrogenation of the azepine (**116**) to the dihydro derivative (**117**)[187] as shown in Scheme 7.



116 **117**

Scheme 7. Partial catalytic hydrogenation of the azepine (**116**).

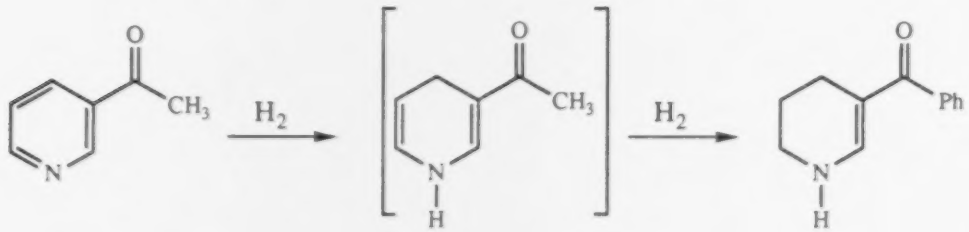
Furthermore, partial hydrogenation of pyridine rings containing 3-acyl, formyl, keto, cyano, and other functions have been reported.[188,189,190] For example, Lyle and Mallet[188] have described the partial hydrogenation of the 1-alkyl-3-benzoylpyridinium salt **118** to give the corresponding tetrahydropyridine **119** in which the C5-C6 double bond was preferentially reduced (Scheme 8).



118 **119**

Scheme 8. Partial hydrogenation of the 1-alkyl-3-benzoylpyridinium salt (**118**) to give the tetrahydropyridine (**119**).

Freidfelder[189] has reported the partial hydrogenation of 3-acetylpyridine (**120**) to the corresponding tetrahydropyridine (**122**). It was proposed that the formation of **122** probably takes place by 1,4-addition, giving the intermediate **121**. Freidfelder observed that the isolated C5-C6 double bond was reduced preferentially relative to the 2,3-conjugated bond to yield **122** (Scheme 9).



120 **121** **122**

Scheme 9. Preferential hydrogenation of the isolated C5-C6 double bond of (**120**) relative to the C2-C3 configurated double bond.

Electronic effects could also be responsible for the reluctance of the C2-C3 olefinic moiety of **91b** to undergo hydrogenation. The C2-C3 double bond is conjugated with the carbonyl of the 3-benzoyl group and so resonance can occur, thereby deactivating the C2-C3 double bond. In fact, the C3-CO_2Me bond of the calcium channel antagonist 2,6-dimethyl-3,5-dicarbomethoxy-4-phenyl-1,4-dihydropyridine (**123**) has been found through X-ray crystallographic studies[191] to be shorter than the C2-C3 bond, suggesting double bond character for the C3-CO_2Me bond (Figure 9).

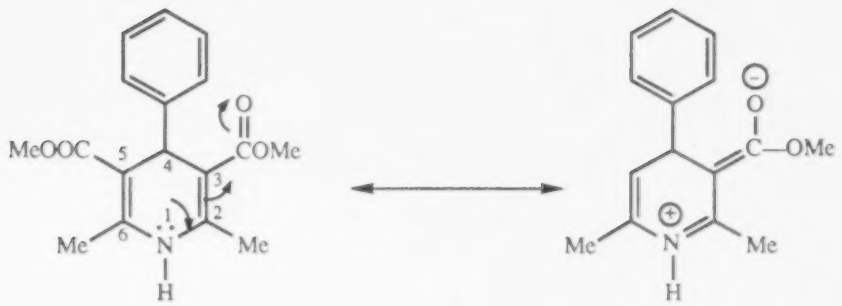


Figure 9. Deactivation of C2-C3 conjugated double bond by resonance.

3.1.7.0.0.0. Synthesis of Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (125-128), Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (129-131), and 2-Methyl-2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dibromo-2-azabicyclo-[4.1.0]hept-3-ene)]acetamide (132)

It has been reported that the C-C bonds in cyclopropane rings resemble olefinic double bonds.[192] The hybridization of cyclopropyl bonds is intermediate in character between sigma (σ) and pi (π) bonds. The C-C bonds in cyclopropane mimic a C=C bond in their ability to conjugate with an adjacent olefinic bond,[193] but unlike a C=C bond, it does not transmit electronic effects.[194] Also, the hybridization of the cyclopropane bonds are considered to result in a higher electron density for the C-C bonds. Furthermore, the cyclopropyl moiety interacts with neighbouring π-electron systems and p-electron centers similar to a vinyl group.[195,196] It was therefore anticipated that a cyclopropyl substituent could act as a biological isostere of the C5-C6 double bond present in compound **91b**. In addition, the hydrophobic halogen substituents F, Cl, and Br are expected to increase the lipophilicity of these compounds. In fact, some halocyclopropyl analogs of 2'-deoxyuridine have been reported to exhibit antiviral and cytotoxic activity.[197,198]

Thus, dihalocarbene :CX_2, generated *in situ* from the Seyferth reagents[199] $PhHgCX_3$ (X = F, Cl, Br) in refluxing benzene, reacted with **91b** to afford compounds **125-128**.

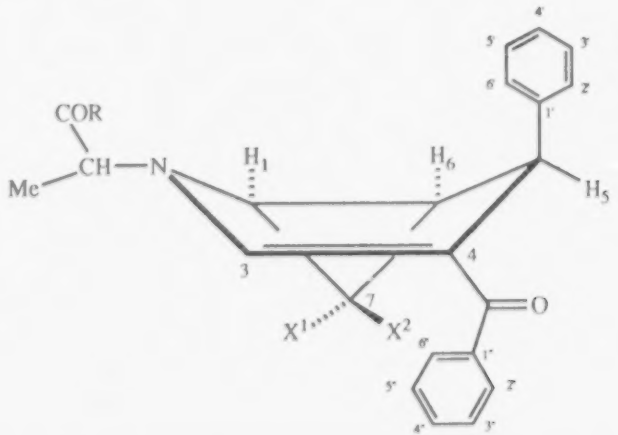
Reactions of **91b** (solid) with phenyl(tribromomethyl)mercury ($PhHgCBr_3$) in dry benzene at 80°C yielded **125**, whereas compound **126** was synthesized from reaction of **91b** with the Seyferth reagent phenyl(bromodichloromethyl)mercury ($PhHgCBrCl_2$). A similar reaction of **91b** with phenyl(trifluoromethyl)mercury[200] ($PhHgCCF_3$) in dry dimethoxyethane in the presence of sodium iodide at 90°C afforded **127** whereas reaction of phenyl(dichlorofluoromethyl)mercury ($PhHgCCl_2F$) with **91b** in refluxing dimethoxyethane yielded **128**.

Monodehalogenation of **125**, **126**, and **128** with tributyltin hydride in the presence of azobisisobutyronitrile (AIBN) as the initiator of the free radical reaction in refluxing benzene afforded compounds **129**, **130**, and **131**, respectively. Ammonolysis of **125**, according to General Procedure C, afforded the corresponding acetamide **132**. These reactions are schematically outlined in Scheme 10. Spectral data for **125-128**, **129-131** and **132** are presented in Table 9 and the physical data is summarized in Table 10.

The ^1H NMR spectra of compounds **125-127** indicate that there is no coupling between H-5 and H-6 which suggests that the dihedral angle between H-5 and H-6 is about 85° based on the Karplus curve.[201]

Carbenes are extremely reactive and give many side reactions, especially insertion reactions which readily reduce yields.[202] Dihalocarbenes however are less reactive than carbenes and so there are no insertion reaction products.[203-205] Most carbenes are electrophilic so electron-withdrawing groups decrease the rate of the reaction,[206,207] as exemplified by the inertness of the C-2–C-3 double bond of **91** to cyclopropanation. Carbenes in the singlet state (which is the most common state) react stereospecifically and syn[208,209] probably by a one-step mechanism.[210] Therefore substituents on the olefin

Table 9. IR and ^{1}H NMR spectral data for methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]-hept-3-ene)]-acetates (**125-128**), methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo[4.1.0]-hept-3-ene)]acetates (**129-131**) and acetamide (**132**).



Entry	X^1	X^2	R	IR cm^{-1}	^{1}H NMR, $CDCl_3$ (δ)[a]
125	Br	Br	OMe	(KBr): 1745 (COO); 1679 (CO); 3105, 3025 (cyclopropyl)	7.2-7.5 (m, 10H, phenyl hydrogens), 7.02 (s, 1H, H-3), 4.26 (s, 1H, H-5), 4.14 (q, J_{CH,CH_3} = 7.2 Hz, 1H, C<u>H</u>CH_3), 3.9 (s, 3H, OMe), 3.4 (d, $J_{1,6}$ = 10.9 Hz, 1H, H-1), 2.46 (d, $J_{1,6}$ = 10.9 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$) δ: 192.45 (benzoyl carbonyl), 171.61 [170.81] (<u>C</u>OOMe), 146.44 [144.42] (C-3), 144.69 (phenyl

(Continued)

Entry	X^1	X^2	R	IR cm^{-1}	^1H NMR, $CDCl_3$ (δ)[a]
125 (Cont'd)	Br	Br	OMe	(KBr): 1745 (COO); 1679 (CO); 3105, 3025 (cyclopropyl)	C-1'), 139.96 (benzoyl C-1"), 130.05 [130.19] (benzoyl C-4"), 128.58-126.46 (other phenyl C-5), 112.89 [113.21] (C-4), 62.37 [61.69] ($N\underline{C}HCH_3$), 52.78 ($COO\underline{C}H_3$), 41.83 [43.52] (C-1), 37.76 [38.24] (C-5), 36.14 (C-6), 32.43 [31.80] (C-7), 16.52 [16.44] ($\underline{C}H_3CH$). Diastereomeric ratio is ≅ 2:1
126	Cl	Cl	OMe	(neat): 1745 (COO); 1679 (CO); 3105, 3025 (cyclopropyl)	7.0-7.42 (m, 10H, phenyl hydrogens), 6.9 (s, 1H, H-3), 4.22 (s, 1H, H-5), 4.02 (q, J_{CH,CH_3} = 7.2 Hz, 1H, $C\underline{H}CH_3$), 3.76 (s, 3H, OMe), 3.26 (d, $J_{1,6}$ = 10.7 Hz, 1H, H-7), 2.24 (d, $J_{1,6}$ = 10.7 Hz, 1H, H-6), 1.56 (d, J_{CH,CH_3} = 7.2 Hz, 3H, $C\underline{H}_3CH$). ^{13}C NMR ($CDCl_3$ δ: 171.56 ($\underline{C}OOMe$), 146.35 (C-3), 144.63 (phenyl C-1'), 139.97 (benzoyl C-1"), 130.04 [130.17] (benzoyl C-4"), 126.31-129.03 (other phenyl C"), 112.70 (C-4), 62.35 [62.17] ($NCHCH_3$), 52.7 ($COO\underline{C}H_3$), 36.85 [37.87] (C-1), 34.14 [35.13] (C-5), 32.56 [32.43] (C-6), 29.66 (C-7), 16.29 [16.64] (CH_3CH)

(Continued)

Entry	X^1	X^2	R	IR cm^{-1}	^1H NMR, $CDCl_3$ (δ)[a]
127	F	F	OMe	(neat): 1745 (COO); 1679 (COO); 3105, 3025 (cyclo-propyl)	7.20-7.50 (m, 10H, phenyl hydrogens), 7.16 [7.04] (s, 1H, H-3), 4.44 (s, 1H, H-5), 4.06 [4.04] (two q, J_{CH,CH_3} = 7.2 Hz, 1H total, C<u>H</u>CH_3), 3.80 [3.84] (s, 3H, OCH_3), 3.26 [3.38] (d, $J_{1,6}$ = 11.4 Hz, of d $J_{H1,F}$ = 5.1 Hz, 1H, H-1), 2.20-2.36 (m, 1H, H-6), 1.56 (d, $J_{CH_3,CH}$ = 7.2 Hz, 3H, C<u>H</u>$_3$CH). ^{13}C NMR ($CDCl_3$) δ: 192.85 [192.71] (benzoyl CO), 170.33 [171.15] (<u>C</u>OOMe), 146.45 [146.20] (C-3), 144.91 [144.81] (phenyl C-1'), 139.92 [139.84] (benzoyl C-1"), 130.04 [129.92] (benzoyl C-4"), 126.39-127.20 (other phenyl C), 112.49 [112.15] (C-4), 109.73 [109.83] (t, $J_{F,C}$ = 296 Hz, C-7), 62.47 [61.94] (N<u>C</u>HCH_3), 52.47 (COO<u>C</u>H_3), 35.18-34.88 [34.73-34.43] (C-1), 31.06 (C-5), 29.94 [29.79] (C-6), 15.90 [15.38] (CH<u>C</u>H_3) ^{19}F NMR (C_6F_6) δ: 37.2 (d, J_{F1F2} = 160.7 Hz of d, $J_{H,F}$ (*cis*) = 15.4 Hz, 1F, F-2); [35.8 (d, $J_{F1,F2}$ = 160.7 Hz of d, $J_{H,F}$ (*cis*) = 14.5 Hz, 1F, F-2], 12.88 (d, $J_{F1,F2}$ = 160.7 Hz, 1F, F-1), [13.07 (d, $J_{F1,F2}$ = 160.7 Hz, 1F, F-1)]. Diastereomeric ratio of 5:4.

(Continued)

Entry	X^1	X^2	R	IR cm^{-1}	^1H NMR, $CDCl_3$ (δ)[a]
128	Cl	F	OMe	(neat): 1745 (COO); 1679 (CO); 3105, 3025 (cyclopropyl)	7.2-7.5 (m, 10H, phenyl hydrogens), 7.0 [7.06] (s, 1H, H-3), 4.48 [4.30] (s, 1H, H-5), 4.08 (q, J_{CH,CH_3} = 7.2 Hz, 1H, C<u>H</u>CH_3), 3.90 [3.88] (s, 3H, OCH_3), 3.44 (d, $J_{1,6}$ = 12.6 Hz, of d, $J_{F,1}$ = 7.2 Hz, 1H, H-1), [3.20 (d, $J_{1,6}$ = 12.6 Hz, 1H, H-1)], 2.38 (d, $J_{f,6}$ = 20.4 of d, $J_{6,F}$ = 7.2 Hz, 1H, H-6)], 1.62 [1.56] (d, $J_{CH_e,CH}$ = 7.2 Hz, 3H, C<u>H</u>$_3$CH). Diastereomeric ratio is 5:4.
129	H	Br	OMe	(neat): 1745 (COO); 1679 (CO); 3105, 3025 (cyclopropyl)	7.2-7.5 (m, 10H, phenyl hydrogens), 7.0 [6.9] (s, 1H, H-3), 4.46 (s, 1H, H-5), 4.02 (q, J_{CH,CH_3} = 7.0 Hz, 1H, C<u>H</u>CH_3), 3.78 [3.80] (s, 3H, OCH_3), 2.68-2.80 (m, 1H, H-7), 1.45-1.7 (m, 5H, CHC<u>H</u>$_3$, H-1, H-6). ^{13}C NMR ($CDCl_3$) δ: 193.37 (benzoyl CO), 171.23 (<u>C</u>$OOCH_3$), 147.15 (C-3), 140.58 (benzoyl C-1"), 129.68 (benzoyl C-4"), 125.91-128.48 (other phenyl C's), 113.0 (C-4), 62.35 [62.08] (N<u>C</u>HCH_3), 52.35 (COO<u>Me</u>), 36.17 (C-1), 30.12 (C-5), 21.71 (C-6), 16.52 (<u>C</u>HBr), 15.35 (CH<u>C</u>H_3). Diastereomeric ratio is 4:1.

(Continued)

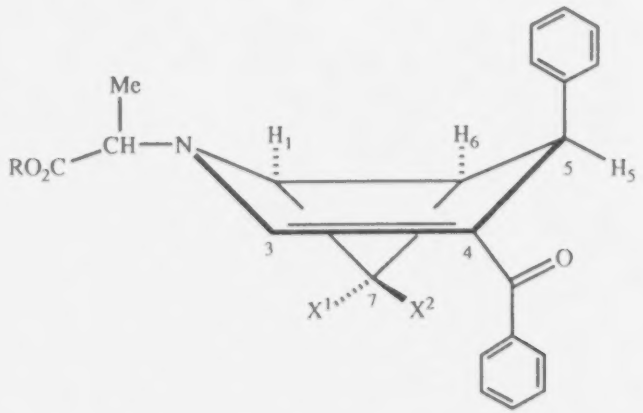
Entry	X^1	X^2	R	IR cm^{-1}	^1H NMR, $CDCl_3$ (δ)[a]
130	H	Cl	OMe	($CHCl_3$): 1745 (COO); 1679 (CO); 3105, 3025 (cyclopropyl)	7.1-7.5 (m, 10H, phenyl hydrogens), 7.02 (s, 1H, H-3), 4.13 (s, 1H, H-5), 4.08 (q, J_{CH,CH_3} = 7.0 Hz, 1H, C<u>H</u>CH_3), 3.78 [3.74] (s, 3H, OCH_3), 3.24 (d, $J_{6,7}$ = 8.5 Hz of d, $J_{1,7}$ = 5.5 Hz, 1H, H-7), 2.92 [2.88] (d, $J_{1,6}$ = 9.9 Hz of d, $J_{1,7}$ = 5.5 Hz, 1H, H-1), 1.8 (d, $J_{1,6}$ = 9.9 Hz of d, $J_{6,7}$ = 8.5 Hz, 1H, H-6), 1.56 [1.48] (d, J_{CH_3CH} = 7.2 Hz, 3H, C<u>H</u>$_3$CH). ^{13}C NMR ($CDCl_3$) δ: 193.0 (benzoyl CO), 171.77 (<u>C</u>OOMe), 148.18 [146.36] (C-3), 146.08 (phenyl C-1'), 140.60 (benzoyl C-1"), 129.83 [129.69] (benzoyl C-4), 128.61-126.04 (other phenyl C's), 113.24 (C-4), 62.65 (61.45] (N<u>C</u>HCH_3), 52.58 (CO_2<u>Me</u>), 38.84 [38.66] (C-1), 33.42 (C-7), 31.65 (C-5), 24.94 [24.61] (C-6), 16.14 [15.82] (<u>C</u>HCH_3). Diastereomeric ratio is 6:1.
131	H	F	OMe	(neat): 1745 (COO); 1679 (CO); 3016, 3025 (cyclopropyl)	7.18-7.60 (m, 10H, phenyl hydrogens), 7.14 (s, 1H, H-3), 4.64 (d, $J_{F,H7}$ = 6.6 Hz of d, $J_{6,7}$ = 9.2 Hz of d, $J_{1,7}$ = 3.8 Hz, 1H, H-7), 4.38 [4.36] (s, 1H, H-5), 4.1 [4.08] (q, J_{CH,CH_3} = 7.2 Hz,

(Continued)

Entry	X^1	X^2	R	IR cm^{-1}	^1H NMR, $CDCl_3$ (δ)[a]
131 (Cont'd.)	H	F	OMe	(neat): 1745 (COO); 1679 (CO); 3016, 3025 (cyclopropyl)	1H, $CHCH_3$), 3.84 [3.80] (s, 3H, OCH_3), 2.82 [2.76] (d, $J_{1,6}$ = 12.7 Hz of d, $J_{1,7}$ = 3.8 Hz of d, $J_{1,F}$ = 3.8 Hz, 1H, H-1), 1.5-1.7 (m, $J_{CH_3,CH}$ = 7.2 Hz, 4H, $\underline{C}H_3CH$, H-6). Minor diastereomer is listed in brackets. Diastereomeric ratio is 3:1.
132	Br	Br	NH_2	(KBr): 1693 (CONH); 1679 (CO); 3322, 3180 (NH_2); 3105, 3025 (cyclopropyl)	7.1-7.4 (m, 10H, phenyl), 7.08 [7.10] (s, 1H, H-3), 6.82 [7.52] (s, 2H, NH_2), 4.10 [4.20] (q, J_{CH,CH_3} = 7.2 Hz, 1H, $C\underline{H}CH_3$), 4.06 (s, 1H, H-5), 3.7 [3.44] (d, $J_{1,6}$ = 10.6 Hz, 1H, H-1), 2.28 [2.26] (d, $J_{1,6}$ = 10.6 Hz, 1H, H-6), 1.56 [1.4] (d, $J_{CH_3,CH}$ = 7.2 Hz, 3H, CH_3CH). Diastereomeric ratio is 3:1.

[a]Minor diastereomers shown in brackets.

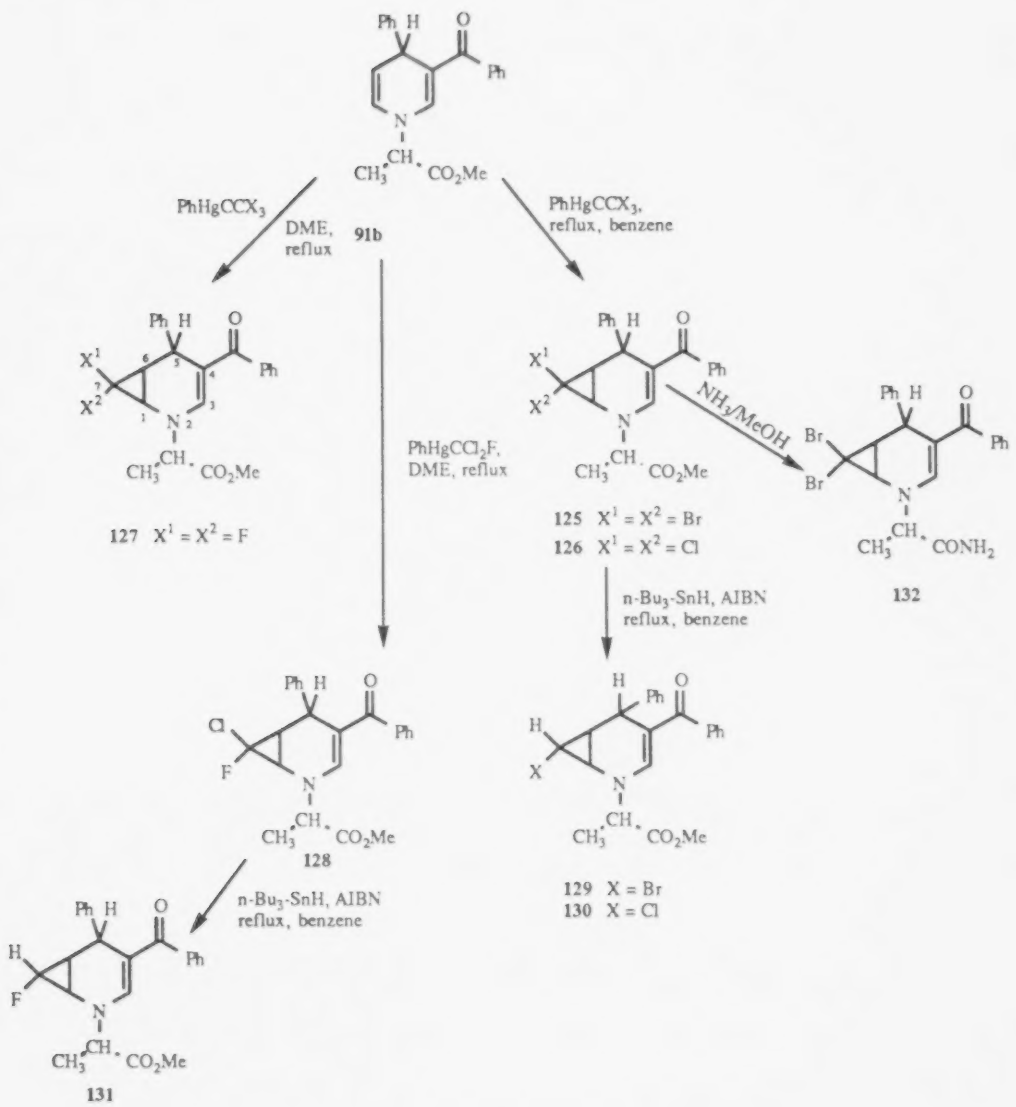
Table 10. Physical data for methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (**125-128**), methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo[4.1.0]-hept-3-ene)]acetates (**129-131**) and acetamide (**132**).



							Microanalysis: Calcd. (Found)		
Entry	X^1	X^2	R	Yield, %	m.p., °C	Formula	C	H	N
125	Br	Br	OMe	50	148-150	$C_{23}H_{21}Br_2NO_3$	53.20 (53.49)	4.08 (3.96)	2.70 (2.71)
126	Cl	Cl	OMe	33	142-145	$C_{23}H_{21}Cl_2NO_3 \cdot 1/2H_2O$	63.47 (63.64)	4.92 (4.90)	3.25 (3.27)
128	Cl	F	OMe	64	oil	$C_{23}H_{21}ClFNO_3 \cdot 3/2H_2O$	62.73 (62.80)	4.77 (5.02)	3.18 (3.16)
130	H	Cl	OMe	31	oil	$C_{23}H_{22}ClNO_3 \cdot 2H_2O$	64.04 (63.92)	5.10 (5.37)	3.25 (3.29)
132	Br	Br	NH_2	50	132-135	$C_{22}H_{19}Br_2N_2O_2$	52.41 (52.67)	4.00 (4.01)	5.56 (5.54)

(Continued)

Entry	X^1	X^2	R	Yield, %	m.p., °C	Formula	Exact Mass	
							Calcd	Found
127	F	F	OMe	53	oil	$C_{23}H_{21}F_2NO_3$	397.1489	397.1484
129	H	Br	OMe	36	oil	$C_{23}H_{22}BrNO_3$	439.0783	439.0889
131	H	F	OMe	45	oil	$C_{23}H_{22}FNO_3$	379.1584	379.1581



Scheme 10. Synthesis of methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (**125-128**), methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo-[4.1.0]hept-3-ene)]acetates (**129-131**), and 2-methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dibromo-2-azabicyclo[4.1.0]hept-3-ene)]acetamide (**132**).

should retain their configuration. Dihalocarbenes and carbenoids, which add readily to C=C double bonds, do not generally add to the C=O bond of ordinary aldehydes and lactones.[211] As already discussed in Section 3.1.0.0.0.0, compound **91** exists in a boat shape with the C-4 phenyl axial to the 1,4-dihydropyridyl ring. If addition of the carbenes $:CX_2$ is concerted, then the configuration of the phenyl substituent should not change. When the cyclopropyl is above the plane of the DHP ring there is a strong steric interaction with the axial phenyl substituent (Figure 10).

Attack at the C=C double bond should therefore occur from the lower face of the boat DHP ring if the phenyl substituent is axial since there is much less steric hindrance (Figure 11). Compound **125** synthesized in this way from pure **91b** gave single resonances in both the ^1H NMR and ^{13}C NMR spectra. This further supports the theory that $:CX_2$ addition is stereospecific.

The observation that compound **125** does not exhibit a $J_{5,6}$ coupling ($J_{5,6}$ = 0 Hz) suggests the H5-H6 dihedral angle is about 85°. When $\phi_{5,6} \cong 85°$, the 1,4-DHP ring exists as a flat boat. H-1 and H-6 must be cis to each other since $J_{1,6}$ = 10.9 Hz and the cyclopropane is a fused ring system. For the difluorocyclopropyl compound (**127**), the ^{19}F NMR spectrum indicated that F_1 is shielded, relative to F_2, by the DHP 3,4-double bond and possibly by the benzoyl group (Figure 12). F_1 must be *trans* to both H-1 and H-6 since $J_{F_{1,1}}$ and $J_{F_{1,6}}$ are both zero hertz.

F_2 is at a lower field since it is not shielded by the DHP C-3–C-4 double bond or the benzoyl group. Compound **127** existed as a mixture of two diastereomers in a ratio of 5:4. The ^{19}F NMR spectrum for **127** exhibited two doublets of doublets for F_2 [J_{F_1,F_2} = 160 Hz; J_{H,F_1} = 15.4 Hz (major diastereomer) and J_{H,F_2} = 14.5 Hz (minor diastereomer)] at 37.2 and 35.8 δ, respectively. In contrast, F_1 appeared as two doublets (J_{F_1,F_2} = 160 Hz) at δ 12.8 (major) and 13.07 (minor), respectively. The J_{F_2,H_6} coupling is much larger than the J_{F_2,H_1} coupling constant.

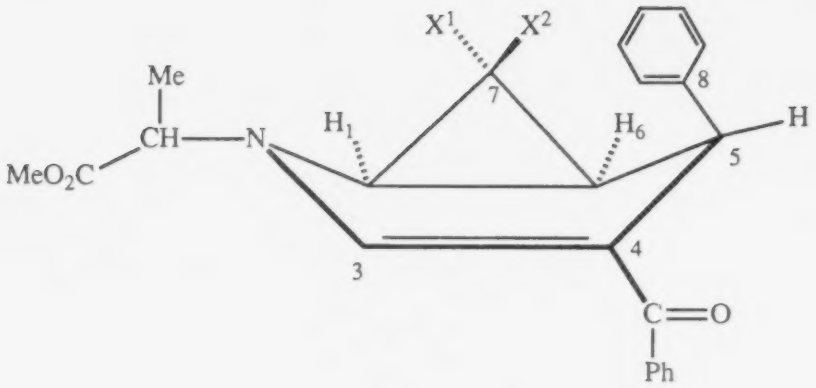


Figure 10. Possible conformation of methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (**125-128**).

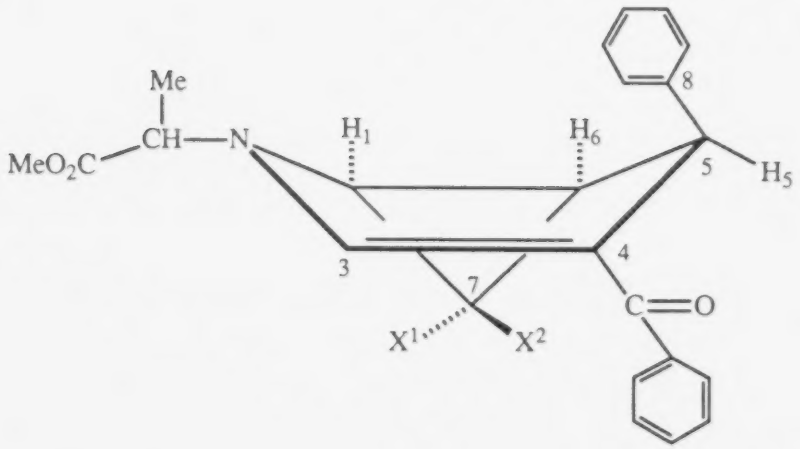


Figure 11. Most stable conformation of methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (**125-128**).

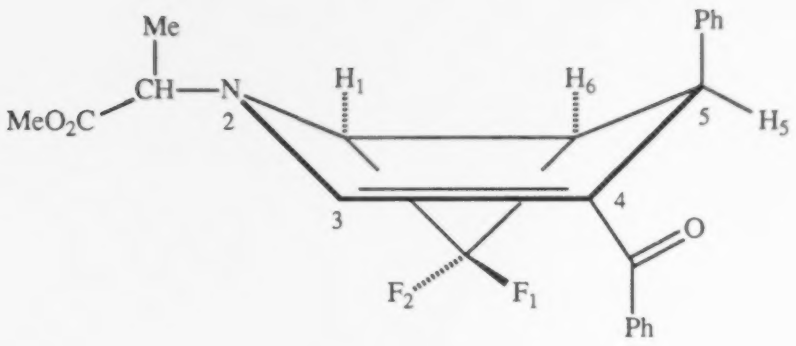


Figure 12. Most probable conformation of methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-difluoro-2-azabicyclo[4.1.0]hept-3-ene)]acetate (**127**).

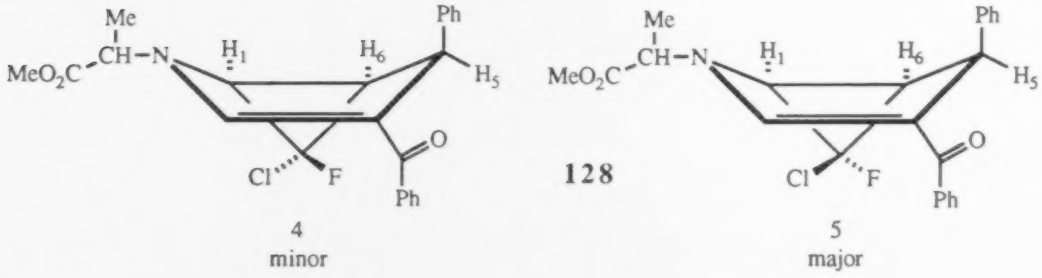


Figure 13. Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-fluoro-7-chloro-2-azabicyclo[4.1.0]hept-3-ene)]acetate (**128**) diastereomer.

Compound **128**, which contains an additional chiral center at C-7, exhibited dual resonances for H-1, H-3, H-5, H-6, OMe, and MeCH- protons in a diastereomeric ratio of 5:4. The ^{1}H NMR spectrum for compound **128** indicated that $J_{H1,F}$ = 0 Hz and $J_{H_6,F}$ = 7.2 Hz in the minor diastereomer suggesting F is *trans* to H-1 and H-6. In the major diastereomer, F must be *cis* to both H1 and H6 as indicated by the coupling constants $J_{H_1,F}$ = 7.2 Hz and $J_{H_6,F}$ = 20.4 Hz (Figure 13).

The stereoselectivity observed in the monodehalogenation reactions of **125**, **126**, and **128** is consistent with a reaction mechanism involving preferential attack by the bulky tri-*n*-butyltin radical at the less hindered C-X bond which is *cis* with respect to the cyclopropyl H-1 and H-6 hydrogens, followed by attack by *n*-Bu_3SnH on the resulting radical[212a] from the less hindered site[212b] (Figure 14).

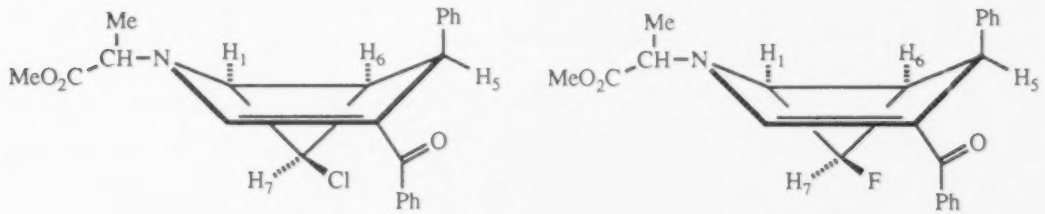


Figure 14. Conformation of methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-chloro-2-azabicyclo[4.1.0]hept-3-ene)]acetate (**130**) and methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-fluoro-2-azabicyclo[4.1.0]-hept-3-ene)]acetate (**131**).

H-1 and H-6 must be *cis* to the new H-7 generated for compound **130** due to the magnitude of the coupling constants observed. In compound **131**, the coupling constants were $J_{1,7}$ = 5.5 (*cis*), $J_{6,7}$ = 8.5 (*cis*) and $J_{1,6}$ = 9.9 Hz with respect to the new generated H-7. The magnitude of the coupling constants observed were $J_{F,H7}$ = 66 Hz, $J_{6,7}$ = 9.2 Hz (*cis*) and $J_{1,7}$ = 3.8 Hz (*cis*).

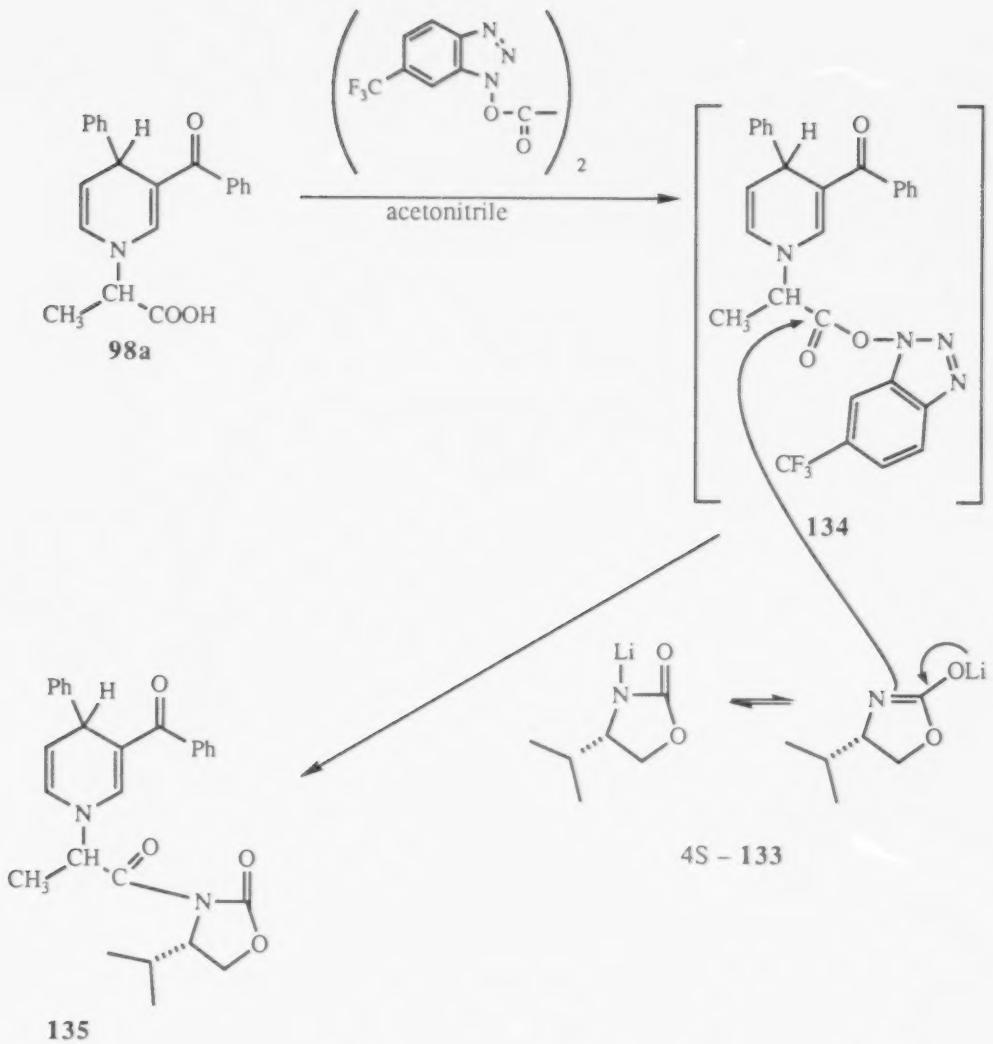
A large number of spectra of substituted cyclopropane derivatives have been reported. The magnitude of the vicinal coupling constant for J_{cis} is always larger than J_{trans} for any given pair of cyclopropyl stereoisomers[213,214] and this was used to assign the orientation, in some cases, of the halogen on the cyclopropane ring. The δ values with respect to each halogen were found to be F > Cl > Br which is consistent with the electronegativity order for F, Cl and Br.

3.1.8.0.0.0. Attempted Synthesis of Chiral N-Substituted 1,4-Dihydropyridine Analogs

When a drug exists as a racemate, or a mixture of diastereomers, higher biological activity is often exhibited by one enantiomer or one diastereomer. Therefore, synthetic methodologies[20] that provide the physiologically more active compounds in optically pure form or as a single diastereomer, are advantageous. Several strategies for the synthesis of chiral arylacetic acids in optically pure form have been reported.[215-219] Attempts were made in this investigation to synthesize pure diastereomers, or enantiomers, in anticipation that a single diastereomer, or enantiomer, might exhibit superior antiinflammatory activity. This rationale is based on the well documented SARs for NSAIDs that generally the active (+)-enantiomer has the (S)-configuration.

3.1.9.0.0.0. Synthesis of 3-Benzoyl-4-phenyl-1-{1-methyl-2-oxo-2-[(4S)-4-isopropyl-2-oxazolidinonyl]ethyl}-1,4-dihydropyridine (135)

The use of Evans's reagent (4S)-4-isopropyl-2-oxazolidinone as a chiral auxiliary for the synthesis of optically active (S)-Ketoprofen, (S)-Ibuprofen and (S)-Naproxen has been reported.[220] Thus, reaction of (4S)-(-)-4-isopropyl-2-oxazolidinone with *n*-butyllithium will give the lithio enolate species **133** which should react readily with the activated ester **134**. The activated ester **134** was prepared from the acid **98a** and the coupling reagent 1,1'-bis[6-trifluoromethyl)benzotriazolyl]oxalate (BTBO) according to the procedure reported by Takeda *et al.*[221] The lithium enolate **133** was then treated with **134** to afford **135** in 33% yield. The reaction pathway and mechanism is outlined in Scheme 11. The diastereomers could not be separated.



Scheme 11. Synthesis of 3-benzoyl-4-phenyl-1-{1-methyl-2-oxo-2-[(4S)-4-isopropyl-2-oxazolidinonyl]ethyl}-1,4-dihydropyridine (**135**).

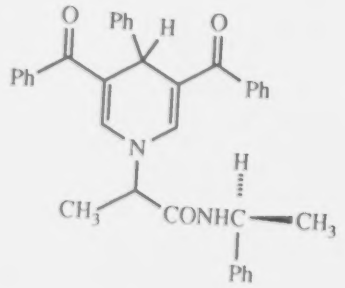
3.1.10.0.0.0. Synthesis of N-[(1S)-1-phenethyl]-2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide Diastereomers (137a and 137b)

The use of (S)-(-)-α-methylbenzylamine as a chiral derivatization agent in the separation of diastereomers of arylpropionic acids has been investigated.[222] Thus, compound **136** was synthesized according to the procedure reported by Takeda *et al.*[221] with the hope that two diastereomers (SS and SR) could be separated and the amide group hydrolyzed to give the respective enantiomers. Reaction of 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acid (**108**) with BTBO in acetonitrile yielded the activated ester **136**, which on reaction with (S)-(-)-α-methylbenzylamine afforded the diastereomers **137a** and **137b** in 38% total yield. The two diastereomers **137a** and **137b** were separated by preparative silica gel TLC. However, attempts to regenerate the free acids by hydrolysis of the amide moiety in either diastereomer was unsuccessful. The hydrolysis reaction was attempted using triethylamine and trichlorosilane which has been reported by Buckle *et al.*[223] to be an efficient method for the hydrolysis. The ^{1}H NMR spectrum of the hydrolysis reaction product indicated disappearance of starting DHP material. It is plausible that $HSiCl_3$, which is a strong Lewis acid, protonates the N-1 position of the DHP with subsequent ring cleavage. The reaction is outlined in Scheme 12. The spectral data for **137a** and **137b** are shown in Table 11.

3.1.11.0.0.0. Synthesis of (S)-Methoxycarbonyl-α-methyl methyl-2-methyl-2-{1-[3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl]-acetate (138)

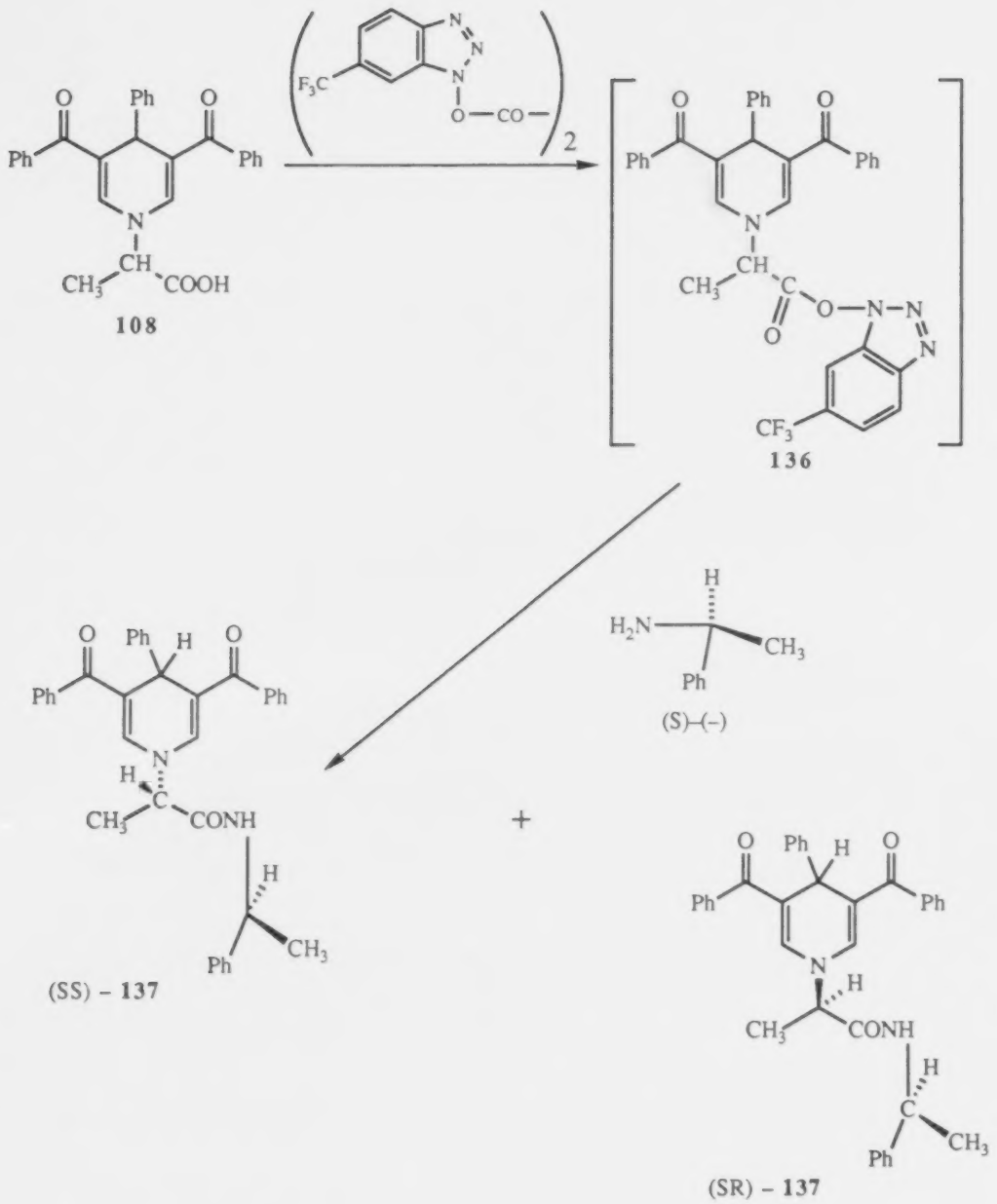
Further attempts directed towards the synthesis of pure diastereomers possessing a chiral lactate ester led to the synthesis of compound **138**. Thus, using the procedure of Takeda *et al.*,[221] a solution of 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acid (**108**) was reacted with a suspension of BTBO in acetonitrile to give

Table 11. ^{1}H NMR spectral data for N-[(1S)-1-phenethyl]-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide diastereomers (**137a** and **137b**).



137a and **137b**

Entry	^{1}H NMR ($CDCl_3$) δ
137a	7.1-7.6 (m, 20H, phenyl hydrogens), 6.90 and 6.96 (two d, $J_{2,6}$ = 1.5 Hz, 1H each, H-2 and H-6), 6.14 (d, $J_{NH,CH}$ = 7.2 Hz, 1H, NH), 5.64 (s, 1H, H-4), 5.1 (q, J_{CH,CH_3} = 7.2 Hz, 1H, C<u>H</u>(CH_3)CO), 1.46 and 1.44 (two d, $J_{CH_3,CH}$ = 7.2 Hz, 6H, two C<u>H</u>$_3$CH)
137b	7.1-7.5 (m, 20H, phenyl hydrogens), 6.90 and 6.92 (two d, $J_{2,6}$ = 1.5 Hz, 1H each, H-2 and H-6), 6.22 (d, $J_{NH,CH}$ = 7.2 Hz, 1H, NH), 5.62 (s, 1H, H-4), 5.1 (q, J_{CH,CH_3} = 7.2 Hz, $J_{CH,NH}$ = 7.2 Hz, NHC<u>H</u>CH_3), 3.9 (q, J_{CH,CH_3} = 7.2 Hz, 1H, C<u>H</u>(CH_3)CO), 1.42 (d, $J_{CH_3,CH}$ = 7.2 Hz, 6H, two C<u>H</u>$_3$CH)



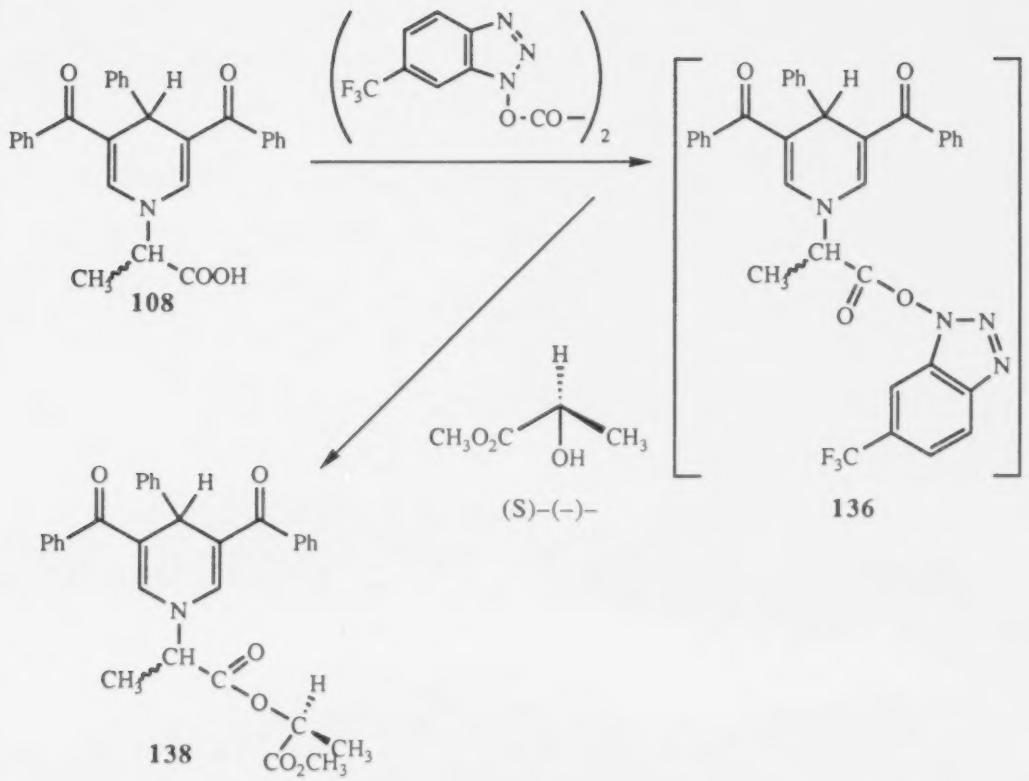
Scheme 12. Synthesis of N-[(1S)-1-phenethyl]-2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide diastereomers (**137a**) and (**137b**).

the activated ester **136** which, without isolation, was reacted with (S)-(-)-methyl lactate. The resulting mixture was worked up as reported[221] to afford **138** as an oil in 12% yield. Activated esters have frequently been prepared by reaction of an acid with N-hydroxy imides[224] or 1-hydroxybenzotriazole[224] in the presence of N,N'-dicyclohexylcarbodiimide (DCC). However, DCC causes side reactions such as formation of N-acylurea and a Lossen rearrangement reaction for N-hydroxysuccinimide.[225] BTBO was used in this investigation since it has been reported that with BTBO, nucleophilic attack by alcohol to active ester occurs stoichiometrically,[221] while excess alcohols are required with benzotriazole[226] and 6-chlorobenzotriazole esters.[227] Furthermore, BTBO is not a skin irritant as is DCC and BTBO esterifications proceed much faster and produce only three by-products, carbon monoxide, carbon dioxide, and 1-hydroxy-6-(trifluoromethyl)benzotriazole.[221] It was expected that the 3,5-dibenzoyl compound **138** could be separated into two pure diastereomers (SS and SR) which could then be cleaved by hydrolysis to afford the pure S and R enantiomers. However **138** was a single band on TLC which could not be separated.

The ^{1}H NMR spectrum of compound **138** indicated a mixture of two diastereomers in the ratio 5:4 which differ in configuration at the N-C<u>H</u>$(CH_3)CO_2$ chiral carbon. The spectrum exhibited dual resonances for the H-2, H-6, NC<u>H</u>CH_3 and OMe protons. The reaction is outlined in Scheme 13.

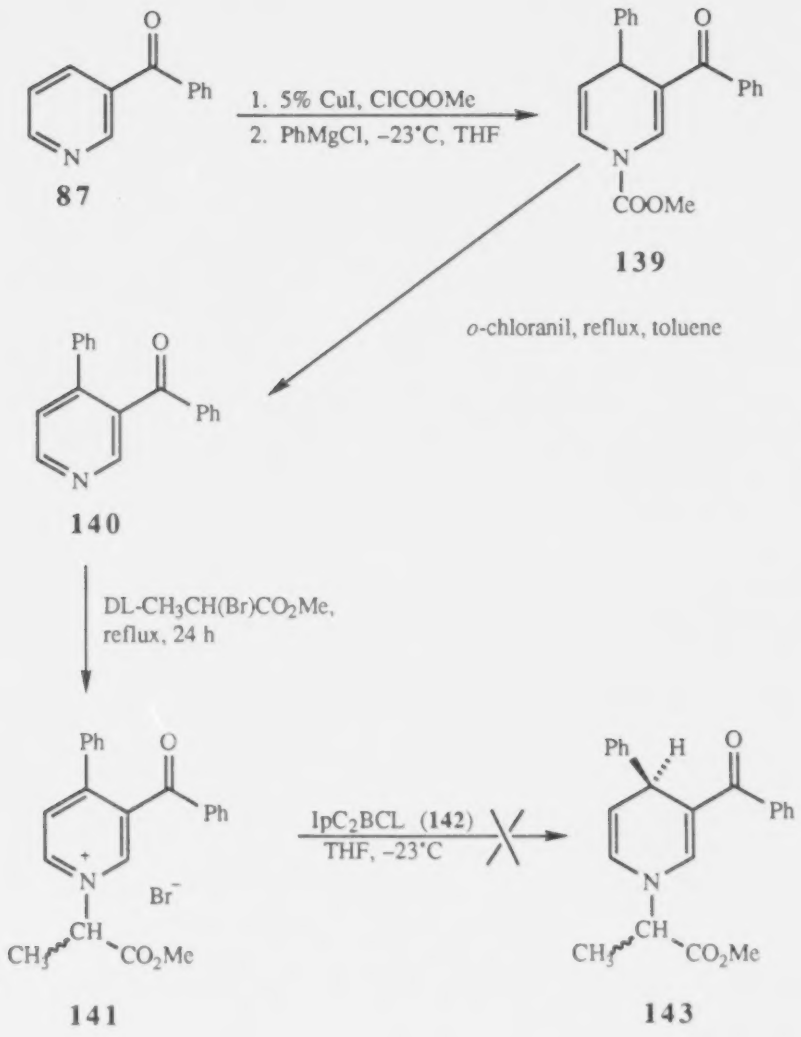
3.1.12.0.0.0. Synthesis of (4S)- or (4R)-Methyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (143)

Diisopinocampheylchloroborane, IpC_2BCl, **142**), reduces ring and chain substituted halo or alkyl ketones to the corresponding haloalcohols in excellent enantiomeric excess.[228] It was therefore anticipated that IpC_2BCl could be used to synthesize **143** by stereoselective addition to the 3-benzoyl-4-phenyl-N-substituted pyridinium salt **141**. The salt



Scheme 13. Synthesis of (S)-methoxycarbonyl-α-methyl methyl-2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetate.

141 was prepared by quaternization of 3-benzoyl-4-phenylpyridine (**140**) in refluxing anhydrous acetone with methyl DL-2-bromopropionate in acetone for 24 h. To a solution of IpC_2BCl in THF at -23°C was added **141**, suspended in THF under nitrogen and the mixture was stirred for 7 h prior to work up as reported.[229] Although silica gel TLC indicated that the starting material **141** was no longer present, the ^1H NMR spectrum of the isolated product was not that of the desired compound. The reaction is outlined in Scheme 14.



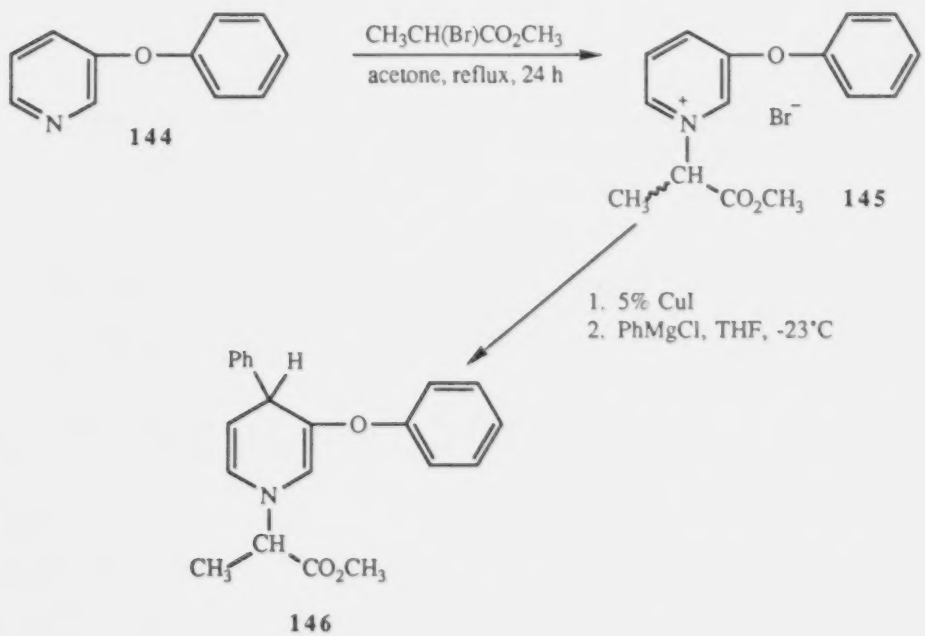
Scheme 14. Attempted synthesis of (4S)- or (4R)-methyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (**143**).

3.1.13.0.0.0. Attempted Synthesis of Methyl 2-methyl-2-[1-(3-phenoxy-4-phenyl-1,4-dihydropyridyl)]acetate (146)

A structural unit common to many useful NSAIDs is the 2-phenylpropionic acid moiety from which the term "profen" drugs is derived. Profen drugs differ in the nature of the substituents on the aromatic ring.[230] Examples include Ibuprofen, Flurbiprofen, Ketoprofen, and Fenoprofen. It was therefore of interest to replace the 2-phenylpropionic

acid moiety with a 1,4-dihydropyridyl acetic acid ester moiety since pyridine and dihydropyridine have been reported to be bioisosteric with phenyl moieties.[40,161,162]

3-Phenoxypyridine (**144**), which was prepared in 84% yield according to the procedure of Renshaw and Conn,[231] was quaternized with methyl DL-2-bromopropionate to afford the N-substituted 3-phenoxypyridinium salt (**145**). The copper catalyzed regiospecific reduction of **145** with phenylmagnesium chloride, as described in General Procedure A, afforded **146** as a brownish oil. The purification of **146** was attempted using silica gel and neutral alumina column chromatography but intensive decomposition occurred. Thus, it was not possible to obtain pure **146**. The instability of compound **146** could be due to the 3-phenoxy group which has been reported[119] to destabilize dihydropyridines. The synthetic procedure used to prepare **146** is outlined in Scheme 15. The compound **146** also decomposed on storage both at 0°C and room temperature.

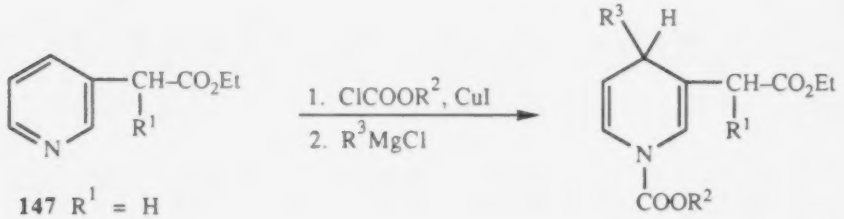


Scheme 15. Syntheis of methyl 2-methyl-2-[1-(3-phenoxy-4-phenyl-1,4-dihydropyridyl)]acetate (**146**).

3.1.14.0.0.0. Synthesis of Ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]acetates (149-152), Ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]-acetate (153), and Ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (154)

The acetic acid side chain of known heteroarylacetic acid NSAIDs is usually attached to an sp^2 hybridized carbon. It has also been established that the pyridine ring and dihydropyridyl ring systems are bioisosteric with respect to antiinflammatory activity.[40,161,162] Thus, it was of interest to extend the SARs by preparing compounds **149-154** for evaluation as antiinflammatory agents.

Thus, quaternization of ethyl 3-pyridylacetate (**147**, R^1 = H), or ethyl 2-methyl-3-pyridylacetate (**148**, R^1 = Me) with phenyl chloroformate (R^2 = Ph) or methylchloroformate (R^2 = Me) and the subsequent copper-catalyzed Grignard reduction of the N-acylpyridinium salts formed, afforded compounds **149-154** in 64 to 96% yield. The reaction procedure is outlined in Scheme 16. The spectral data for **149-154** are shown in Table 12 and the physical data are shown in Table 13.

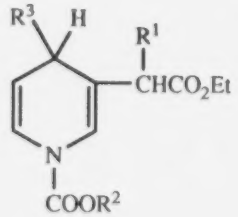


147 R^1 = H
148 R^1 = Me

149 - 154

Scheme 16. Ethyl 2-[3-[(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]acetates (**149-152**), Ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (**153**) and ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (**154**).

Table 12. IR and ^1H NMR spectral data for ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]acetates (**149-152**), ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-1,4-dihydropyridyl)]acetate (**153**), and ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (**154**).



149 – 154

Entry	R^1	R^2	R^3	IR (neat) cm^{-1}	^1H NMR, $CDCl_3$ (δ)
149	H	Ph	Ph	1745 (COOEt); 1730 (COOPh)	7.16-7.48 (m, 10H, phenyl hydrogens), 7.0-7.14 (m, 2H, H-2, H-6), 5.05 and 5.12 (two d, $J_{4,5}$ = 4.0 Hz of d, $J_{5,6}$ = 8.6 Hz, 1H total, H-5), 4.26 and 4.36 (two d, $J_{4,5}$ = 4.0 Hz, 1H, H-4), 4.1 (q, J_{CH_2,CH_3} = 7.0 Hz, 2H, $C\underline{H_2}CH_3$), 2.72-2.92 (m, 2H, $C\underline{H_2}COO$), 1.14-1.32 (m, 3H, $C\underline{H_3}CH$)
150	H	Ph	4ClPh	1745 (COOEt); 1730 (COOPh)	6.8-7.45 (m, 9H, phenyl hydrogens), 6.76 and 6.80 (two s, 1H total, H-2), 6.76 (d, $J_{5,6}$ = 8.6 Hz, 1H, H-6), 5.0 and 5.08 (two d, $J_{5,6}$ and 4.30 (two d, $J_{4,5}$ = 4.0 Hz, 1H total, H-4), 4.08 (q, J_{CH_2,CH_3} = 7.0 Hz, 2H, $C\underline{H_2}CH_3$), 2.7-2.9 (m, 2H, $C\underline{H_2}COO$), 1.24 (t, J_{CH_3,CH_2}= 7.0 Hz, 3H, $C\underline{H_3}CH_2$)

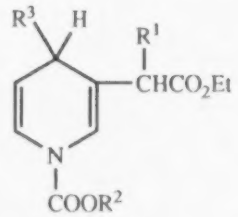
(Continued)

Entry	R^1	R^2	R^3	IR (neat) cm^{-1}	^1H NMR, $CDCl_3$ (δ)
151	H	Ph	n-Bu	1740 (COOEt); 1730 (COOPh)	7.14-7.50 (m, 5H, phenyl hydrogens), 6.86 -7.0 (m, 2H, H-2, H-6), 4.95 and 5.02 (two d, $J_{4,5}$ = 4.9 Hz of d, $J_{5,6}$ = 8.4 Hz, 1H total, H-5), 4.18 (m, 2H, $C\underline{H}_2CH_3$), 3.18-2.92 (m, 3H, $C\underline{H}_2COO$, H-4), 1.2-1.65 (m, 9H, CO_2CH_2, $C\underline{H}_2C\underline{H}_2CH_2CH_3$), 0.88 (t, J = 7 Hz, $CH_2CH_2C\underline{H}_3$)
152	H	Ph	Me	1740 (COOEt); 1730 (COOPh)	7.1-7.45 (m, 5H, phenyl hydrogens), 6.84-6.96 (m, 2H, H-2, H-6), 4.9 and 5.02 (d, $J_{5,6}$ = 8.8 Hz of d, $J_{4,5}$ = 4.3 Hz, 1H total, H-5), 4.19 (q, J_{CH,CH_3} = 7.0 Hz, 2H, $C\underline{H}_2CH_3$), 2.94-3.25 (m, 3H, $C\underline{H}_2CO_2$, H-4), 1.28 (t, 3H, $CH_2C\underline{H}_3$), 1.16 (d, $J_{CH_3,H}$ = 6.9 Hz, 3H, $CHC\underline{H}_3$)
153	Me	Ph	Ph	1742 (COOEt); 1730 (COOPh)	7.1-7.6 (m, 10H, phenyl hydrogens), 6.9-7.1 (m, 2H, H-2, H-6), 5.14 and 5.04 (two d, $J_{5,6}$ = 8.8 Hz of d, $J_{4,5}$ = 4.3 Hz, 1H total, H-5), 4.25 (d, $J_{4,5}$ = 4.3 Hz, 1H, H-4), 4.08 (m, 1H, $C\underline{H}_2CO_2$), 2.9 (q, $J_{CH_3,CH}$ = 7.0 Hz, 1H, $C\underline{H}CH_3$), 1.1-1.45 (m, 6H, $CHCH_3$, CH_2CH_3). Rotameric ratio 1:1.

(Continued)

Entry	R^1	R^2	R^3	IR (neat) cm^{-1}	^1H NMR, $CDCl_3$ (δ)
153 (Cont'd.)	Me	Ph	Ph	1742 (COOEt); 1730 (COOPh)	^1H NMR (Me_2SO-d_6) (68°C): 7.2-7.5 (m, 10H, phenyl hydrogens), 6.98-7.10 (m, 2H, H-2, H-6), 5.12 (d, $J_{5,6}$ = 8.8 Hz of d, $J_{4,5}$ = 4.3 Hz, 1H, H-5), 4.20 (d, $J_{4,5}$ = 4.3 Hz, 1H, H-4), 3.98 and 4.02 (two overlapping q, J = 7 Hz, $C\underline{H}_2CH_3$), 2.96 and 2.29 (two overlapping q, J = 7.0 Hz, 1H, $C\underline{H}CH_3$), 1.06-1.24 (m, 6H, $CH_2C\underline{H}_3$, $CHC\underline{H}_3$)
154	H	Me	Ph	1745 (COOEt); 1740 (COOMe)	7.12-7.3 (m, 5H, phenyl hydrogens), 6.90 and 6.93 (two s, 1H total, H-2), 6.74 and 6.78 (two d, $J_{5,6}$ = 8.6 Hz, 1H total, H-6), 4.85 and 4.95 (two d, $J_{5,6}$ = 8.6 Hz of d, $J_{4,5}$ broadened, 1H total, H-5), 4.16 (broad peak, 1H, H-4), 4.06 (q, J_{CH,CH_3} =7 Hz, 2H, $C\underline{H}_2CH_3$), 3.8 (s, 3H, OCH_3), 2.7 (s, 2H, $C\underline{H}_2COO$), 1.2 (t, J_{CH,CH_3} = 7.0 Hz, 3H, $C\underline{H}_3CH_2$). The rotamer ratio was about 1:1.

Table 13. Physical data for ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]acetates (**149**-**152**), ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-1,4-dihydropyridyl)]acetate (**153**), and ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]-acetate (**154**).



						Microanalysis: Calcd. (Found)		
Entry	R^1	R^2	R^3	Yield,[a] %	Formula	C	H	N
149	H	Ph	Ph	96	$C_{22}H_{21}NO_4$	72.71 (72.77)	5.82 (5.85)	3.85 (3.56)
150	H	Ph	4ClPh	75	$C_{22}H_{20}NO_4$	66.42 (66.30)	5.07 (5.30)	3.52 (3.57)
151	H	Ph	n-Br	82	$C_{20}H_{25}NO_4$	69.94 (69.86)	7.33 (7.26)	4.07 (4.04)
152	H	Ph	Me	64	$C_{17}H_{19}NO_4$	67.75 (67.58)	6.35 (6.37)	4.64 (4.32)
153	Me	Ph	Ph	64	$C_{23}H_{23}NO_4 \cdot 1/2H_2O$	71.50 (71.64)	5.96 (6.16)	3.63 (3.26)
154	H	Me	Ph	87	$C_{17}H_{19}NO_4$	67.76 (67.63)	6.36 (6.05)	4.65 (4.59)

[a]All compounds were oils.

^{1}H NMR variable temperature studies for ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (**153**) indicated that the dual resonances observed for H-2, H-6 and H-5 were due to rotamers in solution. The rotameric ratio was 1:1 for most products at 25°C. The dual resonance peaks for H-5 in compound **153** coalesced at 68°C. The observed rotational isomerism is due to restricted rotation about the nitrogen-to-carbonyl bond of the carbamate moiety present in compounds **149-154** as illustrated in Figure 15 for compound **153**.

153

Figure 15. Rotamers of compound **153** as a result of restricted rotation.

The ^{1}H NMR and IR spectra for compounds **149-154** were consistent with their assigned structures.

3.2.0.0.0.0. PHARMACOLOGICAL SCREENS

3.2.1.0.0.0. Analgesic-Antiinflammatory Structure Activity Relationships (SARs) for Methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates (90a-c), Methyl 2-methyl-2-[(1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates (91-93), 2-[1-(3-Benzoyl-4-substituted-1,4-dihydropyridyl)]acetic Acids (97a-c), 2-Methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic Acids (98a-e), Methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetamides

(99a-c), and 2-Methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetamides (99d-j)

The acetic acid esters (**90-93**), acetic acids (**97-98**) and acetamides (**99**) were synthesized to investigate the effect which replacement of the phenyl ring present in the traditional NSAIDs by a 1,4-dihydropyridyl ring has upon analgesic-antiinflammatory activity. The structures of these 1,4-dihydropyridyl-1-acetic acid esters (**90-93**), acetic acids (**97-98**) and acetamides (**99**) were expected to have some conformational differences relative to the classical aryl acetic acid NSAIDs. For example, the 1,4-dihydropyridine ring system is more puckered than the planar phenyl ring system. While the ene (C=C) moieties of the 1,4-dihydropyridyl ring systems are quasi-planar, there is considerable distortion at the N-1 and C-4 positions. These differences, together with steric effects due to the 1,4-dihydropyridyl N-1 and C-4 substituents were expected to alter the overall volume of the molecule, the distribution of the drug between hydrophilic and hydrophobic tissues, and the interaction of the drug with the antiinflammatory receptor site.[243]

The acetic acid ester (**90-93**), acetic acid (**97-98**) and acetamide (**99**) classes of compounds were investigated to determine the effect of the α-substituent (R^3 = H or Me), the 1,4-dihydropyridyl ring C-4 substituents (R^2 = phenyl, 4-chlorophenyl, 4-tolyl, benzyl, cyclohexyl, *n*-butyl, and iso-butyl), the benzoyl substituent (R^1 = H, Cl, CH_3), and the nature of the N-1 substituent (ester, acid or amide), upon analgesic and anti-inflammatory activities.

In the methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)acetate and methyl 2-methyl-2-[1-(3-benzoyl-4-substituted 1,4-dihydropyridyl)]acetate series (**90-93**), the analgesic activity potency order with respect to the 1,4-dihydropyridyl C-4 R^3 substituent was phenyl (**91**) > iso-butyl (**91h**) > *n*-butyl (**91g**) = 4-chlorophenyl (**90b**) > 4-tolyl (**91d**) > cyclohexyl (**91d**) > benzyl (**91f**). The relative antiinflammatory potency order was phenyl (**91**) > cyclohexyl (**91d**) > 4-chlorophenyl (**91c**) > iso-butyl (**91h**) > *n*-butyl

(**91g**) > benzyl (**91f**) > 4-tolyl (**91d**). The phenyl substituent appeared to be the most active in the series.

The relative order of analgesic activity in the 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acid and 2-methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acid series (**97-98**) was cyclohexyl (**98c**) > phenyl (**97a**) > 4-chlorophenyl (**97b**) > phenyl (**98a**) and the antiinflammatory activity order for this series was phenyl (**98a**) > cyclohexyl (**98c**) > 4-chlorophenyl (**97a**) = phenyl (**98b**).

In the acetamide series, methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]-acetamides (**99a-c**) and 2-methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]-acetamides (**99d-j**), the analgesic activity order was cyclohexyl (**99g**) > phenyl (**99d**) = benzyl (**99h**) > 4-tolyl (**99f**) > 4-chlorophenyl (**99e**) > 4-chlorophenyl (**99b**) ≡ phenyl (**99a**).

The α-substituent (R^3 = H or Me) present in the N-1 acetyl moieties of these compounds also influenced analgesic-antiinflammatory activity. In the ester series (R^4 = OMe), those compounds having R^3 = Me substituents were generally more active than the corresponding R^3 = H analogs. A similar correlation was found for the amide group of compounds. For the acid series (R^4 = OH), the relative activity order was generally, but not always, R^3 = H > Me.

The relative analgesic activity order was generally amide ($R^4 = NH_2$) > ester (R^4 = OMe) > acid (R^4 = OH). This order of activity for the ester, amide and acid analogs could be due to the more lipophilic nature of the ester and amide compounds relative to the acids. The more lipophilic esters may penetrate cell membranes more easily and once inside the cell, hydrolysis to the corresponding acids can occur.

The test results indicate that the R^1 substituent on the benzoyl group influenced analgesic-antiinflammatory activity in the order H = Cl > CH_3 for analgesic activity and H > Cl > CH_3 for antiinflammatory activity. This R^1 substituent activity order could be due to steric factors which might affect drug-receptor interaction.

The pharmacological data for compounds **90-93**, **97-98** and **99** are summarized in Table 14. The most active antiinflammatory agent in this series was **91** which reduced inflammation by 50% at 3 hours and 74% at 5 hours after a 100 mg/kg po dose relative to Ibuprofen which reduced inflammation by 44% at 3 hours and 52% at 5 hours at the same dose. The most active analgesic activity was **99g** (96% inhibition at 50 mg/kg sc dose) relative to Aspirin (58% inhibition at the same dose).

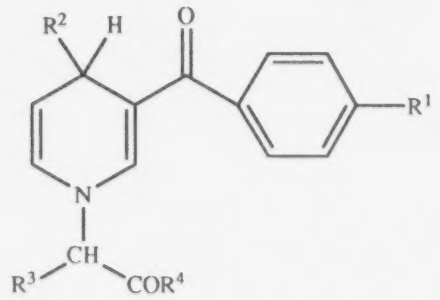
3.2.2.0.0.0. Analgesic-Antiinflammatory SARs of Methyl (103) and Methyl 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetates (104), 2-[1-(3,5-Dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (105), 2-Methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (106) and 2-[1-(3,5-Dibenzoyl-4-phenyl-1,4-dihydropyridyl)]-acetic Acids (107 and 108)

Compounds **103-108** were investigated in order to determine the effect of chirality upon pharmacological activity. Compounds **103**, **105**, and **107** are achiral, whereas compounds **104**, **106**, and **108** have one chiral center when R^1 = Me.

When the analgesic activities were determined, compounds with R^1 = Me were equiactive to the corresponding analogs with R^1 = H. In contrast, the antiinflammatory activity order was R^1 = Me > H. This latter SAR is consistent with known structure-activity correlations for NSAIDs.[244] In general, the order of activity for the R^2 substituent was ester > amide > acid for both analgesic and antiinflammatory activities.

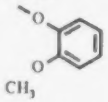
It appears that chirality is a determinant of antiinflammatory activity. Compound **104**, which is chiral, was considerably more active (80% inhibition at 3 h and 71% inhibition at 5 h for a 100 mg/kg po dose) than compound **103**, which is achiral (10% inhibition at 3 h and 80% inhibition at 5 h) for the same dose. Also, compound **104**, which has only one chiral center at the methine carbon of the N-acetyl moiety had superior antiinflammatory

Table 14. Pharmacological data for methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates **90a-90c**; methyl 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates **91a-91h**, **92a-92d**, **93**; *ortho*-methoxyphenyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate **96**; 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acids **97a-97c**; 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acids **98a-98e**; 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetamides **99a-99c**; and 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetamides **99d-99j**.



Entry	R^1	R^2	R^3	R^4	Analgesic Act.,[a] % Inhibition	Antiinflammatory Act.[b], % Inhibition	
						3 h	5 h
90a	H	Ph	H	OMe	45.2 ± 5.7	Inactive	12.9 ± 4.0
90b	H	4-ClC_6H_4	H	OMe	66.0 ± 1.3	44.7 ± 6.5	Inactive
90c	H	4-tolyl	H	OMe	25.5 ± 3.8	18.8 ± 3.8	23.0 ± 5.2
91	H	Ph	H	OMe	94.5 ± 1.5	50.0 ± 7.3	73.6 ± 2.0

(Continued)

Entry	R^1	R^2	R^3	R^4	Analgesic Act.,[a] % Inhibition	Antiinflammatory Act.[b], % Inhibition	
						3 h	5 h
91a	H	Ph	Me	OMe	NT	54.5 ± 3.6	33.7 ± 1.8
91b	H	Ph	Me	OMe	NT	56.1 ± 5.2	61.4 ± 2.4
91c	H	4-ClC_6H_4	Me	OMe	57.5 ± 2.0	48.9 ± 4.7	13.57 ± 3.2
91d	H	4-tolyl	Me	OMe	65.4 ± 2.1	13.9 ± 2.4	2.93 ± 3.7
91e	H	cyclohexyl	Me	OMe	62.8 ± 1.8	63.6 ± 2.4	29.3 ± 3.7
91f	H	benzyl	Me	OMe	57.5 ± 3.7	25.6 ± 3.8	7.3 ± 5.2
91g	H	n-Bu	Me	OMe	66.5 ± 1.4	40.4 ± 3.8	52.7 ± 3.2
91h	H	i-Bu	Me	OMe	72.8 ± 3.1	46.1 ± 1.5	26.4 ± 5.3
92a	Cl	Ph	Me	OMe	80.0 ± 2.5	46.9 ± 4.2	48.5 ± 3.1
92b	Cl	4-ClC_6H_4	Me	OMe	47.6 ± 3.5	Inactive	30.3 ± 2.8
92c	Cl	benzyl	Me	OMe	53.0 ± 2.6	Inactive	38.0 ± 3.0
92d	Cl	cyclohexyl	Me	OMe	51.0 ± 5.3	3.0 ± 2.9	32.0 ± 5.2
93	CH_3	Ph	Me	OMe	62.7 ± 1.7	12.1 ± 2.3	Inactive
96	H	Ph	Me		83.0 ± 4.8	45.5 ± 3.9	50.0 ± 3.6

(Continued)

Entry	R^1	R^2	R^3	R^4	Analgesic Act.,[a] % Inhibition	Antiinflammatory Act.[b], % Inhibition	
						3 h	5 h
97a	H	Ph	H	OH	45.1 ± 0.2	Inactive	Inactive
97b	H	4-ClC_6H_4	H	OH	43.4 ± 2.1	29.7 ± 4.7	Inactive
97c	H	4-tolyl	H	OH	NT	NT	NT
98a	H	Ph	Me	OH	30.1 ± 4.7	14.20 ± 1.3	68.5 ± 0.8
98b	H	4-ClC_6H_4	Me	OH	43.4 ± 2.1	29.7 ± 4.7	Inactive
98c	H	cyclohexyl	Me	OH	62.8 ± 1.8	63.6 ± 5.4	41.9 ± 2.6
98d	H	benzyl	Me	OH	NT	NT	NT
98e	H	n-Bu	Me	OH	NT	NT	NT
98f	H	i-Bu	Me	OH	NT	NT	NT
99a	H	Ph	H	NH_2	33.3 ± 3.2	Inactive	16.0 ± 3.6
99b	H	4-ClC_6H_4	H	NH_2	34.2 ± 5.2	40.4 ± 2.3	Inactive
99c	H	4-tolyl	H	NH_2	NT	NT	NT
99d	H	Ph	Me	NH_2	75.9 ± 2.3	14.3 ± 2.5	68.6 ± 3.0
99e	H	4-ClC_6C_4	Me	NH_2	59.3 ± 2.7	31.2 ± 2.6	Inactive

(Continued)

Entry	R^1	R^2	R^3	R^4	Analgesic Act.,[a] % Inhibition	Antiinflammatory Act.[b], % Inhibition	
						3 h	5 h
99f	H	4-tolyl	Me	NH_2	62.5 ± 5.7	8.3 ± 4.6	60.9 ± 3.5
99g	H	cyclohexyl	Me	NH_2	95.6 ± 3.6	Inactive	Inactive
99h	H	benzyl	Me	NH_2	75.5 ± 2.9	25.0 ± 4.8	18.4 ± 3.9
99i	H	n-Bu	Me	NH_2	NT	NT	NT
99j	H	i-Bu	Me	NH_2	NT	NT	NT
Ibuprofen					–	43.8 ± 2.3	51.7 ± 3.6
Aspirin					57.8 ± 2.8	–	–

NT = Not tested

[a]The result is the mean value ± SEM (n = 5) for a 50 mg/kg sc dose in the 4% NaCl-induced writhing test.

[b]The result is the mean value ± SEM (n = 4) for a 100 mg/kg po dose in the carrageenan-induced edema test.

[c]Tested as a mixture of the oil **91a** and solid **91b**.

[d]Tested as an oil.

[e]Tested as a solid.

activity relative to compound **91** which has two chiral centers at C-4 and the methine carbon.

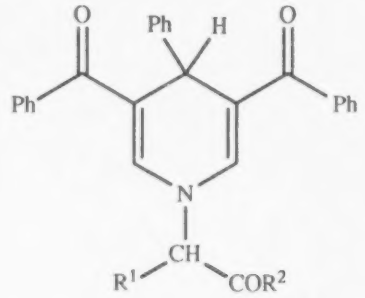
The pharmacological data for compounds **103-108** are summarized in Table 15. The most active analgesic agent in this series was **104** (75% inhibition at 50 mg/kg sc dose relative to Aspirin (58% inhibition at the same dose). Compound **104** was also the most potent antiinflammatory agent (80% inhibition at 3 h and 71% inhibition at 5 h at 100 mg/kg po dose) relative to Ibuprofen (44% inhibition at 3 h and 52% inhibition at 5 h at the same dose).

3.2.3.0.0.0. Analgesic-Antiinflammatory Activity of Methyl 2-methyl-2-(1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydropyridyl)]acetate (113)

The effect of the bioisosteric replacement of a 1,4-dihydropyridyl ring system by a tetrahydropyridyl group was investigated. The tetrahydropyridyl compound (**113**) was more active (78% inhibition at 3 h for a 100 mg/kg po dose) than its 1,4-dihydropyridyl analog (**91**) (50% inhibition at 3 h) when evaluated for antiinflammatory activity. However, compound **91** was more active as an analgesic agent (95% inhibition at 50 mg/kg sc dose) than its tetrahydropyridyl analog (**125**) (69% inhibition at 50 mg/kg sc dose).

The test results suggest that compound **113** may have a rapid onset of antiinflammatory activity and shorter duration of action since antiinflammatory activity was considerably higher at 3 h relative to 5 h, compared to compound **91** which may have a slower onset of action and a longer duration of action. The pharmacological data for compound **113** is presented in Table 16.

Table 15. Pharmacological data for methyl (**103**) and methyl 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetates (**104**), 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (**105**), 2 methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (**106**) and 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acids (**107** and **108**).

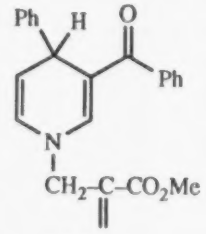


Entry	R^1	R^2	Analgesic Act.,[a] % Inhibition	Antiinflammatory Act.[b], % Inhibition	
				3 h	5 h
103	H	OMe	74.0 ± 6.2	10.0 ± 2.5	8.0 ± 3.5
104	Me	OMe	75.0 ± 2.5	80.0 ± 3.5	70.7 ± 4.8
105	H	NH_2	59.8 ± 13.7	23.5 ± 4.0	26.9 ± 5.0
106	Me	NH_2	52.0 ± 3.8	60.4 ± 2.2	68.2 ± 1.5
107	H	OH	34.6 ± 7.4	22.2 ± 3.04	21.9 ± 2.7
108	Me	OH	48.0 ± 3.9	56.3 ± 5.3	51.2 ± 4.5

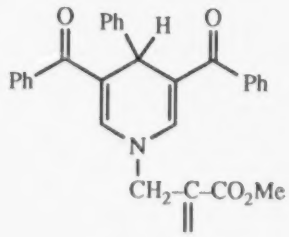
[a]The result is the mean value ± SEM (n = 5) for a 50 mg/kg sc dose in the 4% NaCl-induced writhing test.

[b]The result is the mean value ± SEM (n = 4) for a 100 g/kg po dose in the carrageenan-induced edema test.

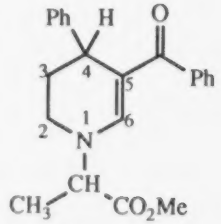
Table 16. Pharmacological data for methyl 2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**111**), methyl 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**112**), and methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydropyridyl)]acetate (**113**).



111



112



113

Entry	Analgesic Act.,[a] % Inhibition	Antiinflammatory Act.[b], % Inhibition	
		3 h	5 h
111	60.0 ± 3.8	30.0 ± 5.6	10.5 ± 4.2
112	48.0 ± 2.3	15.3 ± 3.5	28.0 ± 3.8
113	68.6 ± 5.0	78.0 ± 4.8	23.0 ± 4.2

[a]The result is the mean ± SEM (n = 5) for a 50 mg/kg sc dose (n = 5) determined using the NaCl-induced writhing test.

[b]The result is the mean ± SEM (n = 4) for a 100 mg/kg po dose (n = 4) determined using the carrageenan-induced edema test.

3.2.4.0.0.0. Analgesic-Antiinflammatory Activity of Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (125-128)

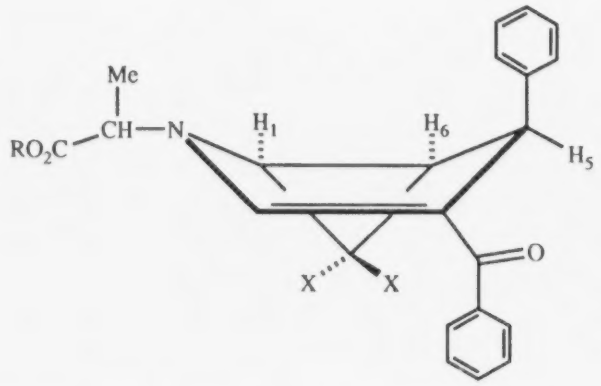
The effect which replacement of the C5-C6 double bond of **91** with a dihalocyclopropyl moiety has upon biological activity was investigated (Table 17). With respect to the halogen substituents, the antiinflammatory potency order was $Br_2 > Cl_2 > F_2 > ClF$, whereas the analgesic activity order was $Cl_2 > Br_2 > F_2 > ClF$. The cyclopropyl moiety in general reduced analgesic-antiinflammatory compared to the corresponding dihydropyridyl analog. This reduced activity could be due to the change in the overall volume of the cyclopropyl compounds with respect to interaction at the receptor site.

3.2.5.0.0.0. Analgesic-Antiinflammatory SARs for Ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]acetates (151-152), Ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (153) and Ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (154)

The analgesic activity test results (Table 18) indicated that the order of activity for the R^3 substituent was Ph (**149**) > Me (**152**) > *n*-Bu (**151**) > 4-chlorophenyl (**150**). The α-methyl substituent also had an effect on analgesic activity with R^1 = H exhibiting superior activity to a R^1 = Me substituent. The R^2 substituent was also a determinant of analgesic activity with R^2 = Ph (**149**) > Me (**154**) [**149** (R^2 = Ph) > **154** (R^2 = Me)]. The antiinflammatory activity order for the R^3 substituent was *n*-Bu (**151**) > Me (**152**) > phenyl (**149**) > *p*-chlorophenyl (**150**) whereas the R^1 substituent potency order was R^1 = Me (**153**) > H (**149**).

The most active analgesic agent in this series was **149** (83% inhibition at 50 mg/kg sc dose) relative to Aspirin (58% inhibition at the same dose) whereas the most potent anti

Table 17. Pharmacological data for methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (**125-128**), methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo[4.1.0]-hept-3-ene)]acetates (**129-131**) and acetamide (**132**).



Entry	X^1	X^2	R	Analgesic Act.,[a] % Inhibition	Antiinflammatory Act.[b], % Inhibition	
					3 h	5 h
125	Br	Br	OMe	68.3 ± 2.9	62.5 ± 3.2	41.0 ± 1.6
126	Cl	Cl	OMe	75.2 ± 1.8	50.3 ± 6.5	35.6 ± 2.3
127	F	F	OMe	56.5 ± 2.1	42.3 ± 1.5	28.5 ± 3.3
128	Cl	F	OMe	36.9 ± 1.8	32.9 ± 2.5	30.6 ± 2.5

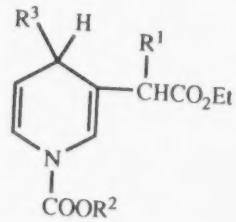
(Continued)

Entry	X^1	X^2	R	Analgesic Act.,[a] % Inhibition	Antiinflammatory Act.[b], % Inhibition	
					3 h	5 h
130	H	Cl	OMe	–	–	–
131	H	F	OMe	–	–	–
132	Br	Br	NH_2	82.5 ± 2.8	48.5 ± 2.8	68.2 ± 1.6

[a]The result is the mean ± SEM (n = 5) for a 50 mg/kg sc dose in the NaCl-induced writhing test.

[b]The result is the mean ± SEM (n = 4) for a 100 mg/kg po dose in the carrageenan-induced edema test.

Table 18. Pharmacological data for ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]acetates (**149-152**), ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-1,4-dihydropyridyl)]acetate (**153**), and ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (**154**).



Entry	R1	R2	R3	Analgesic Act.,[a] % Inhibition	Antiinflammatory Act.[b], % Inhibition, 5 h	
					3 h	5 h
149	H	Ph	Ph	83.1 ± 3.8	50.2 ± 3.5	31.7 ± 1.5
150	H	Ph	4ClPh	62.4 ± 5.2	7.3 ± 4.8	6.0 ± 2.8
151	H	Ph	n-Bu	73.2 ± 2.6	62.3 ± 2.3	35.4 ± 1.8
152	H	Ph	Me	80.2 ± 2.4	60.3 ± 3.2	37.3 ± 4.5
153	Me	Ph	Ph	68.0 ± 1.5	70.5 ± 3.5	45.8 ± 1.6
154	H	Me	Ph	58.0 ± 2.5	46.0 ± 1.5	38.0 ± 2.8

[a]The result is the mean ± SEM (n = 5) for a 50 mg/kg sc dose in the NaCl-induced writhing test.

[b]The result is the mean ± SEM (n = 4) for a 100 mg/kg po dose in the carrageenan-induced edema test.

inflammatory agent in the series was (**153**) which reduced inflammation by 76% at 3 h and 46% at 5 h for a 100 mg/kg po dose relative to Ibuprofen which reduced inflammation by 44% at 3 h and 52% at 5 h at the same dose.

3.3.0.0.0.0. ANALGESIC ACTIVITY EVALUATION

A variety of analgesic tests are used which differ from each other by the nature of the stimuli, parameters, sites of application, nature of responses, quantitation, and apparatus. These tests can be classified into chemical, electrical, mechanical, and thermal methods. Chemically induced animal writhing assays are common protocols used for analgesic activity evaluation. A variety of chemical agents have been used to produce pain, including acetic acid,[232] acetylcholine,[233] hypertonic saline,[234] phenylquinone,[235] serotonin,[236] and bradykinin.[237] The intraperitoneal administration of a noxious chemical substance to mice and rats produces peritoneal irritation, which elicits a writhing response characterized by internal rotation of the feet, sucking in of the stomach, elongation of the body, arching of the back, rolling on one side, and circling the cage.[238]

The phenylquinone-induced writhing test in mice is the most extensively used writhing assay, but it gives false positive results for some compounds.[237] In addition, repeated challenge using phenylquinone at short time intervals is not possible. Therefore, the time course of drug action cannot be determined using this assay. Chronic phenylquinone challenges may also cause damage to abdominal organs.

The NaCl-induced writhing assay used in this investigation, described by Fukawa *et al.*[239] is reported to be highly specific with no incidence of false positives. Hypertonic sodium chloride solution (4%, w/w, 1 M) was found to be the most reliable agent from a number of noxious irritants evaluated in rats.[234] The 4% sodium chloride-induced writhing assay also has advantages that repeated challenges at short intervals (15 minutes) are possible and chronic challenges do not cause damage to abdominal organs.[239]

Analgesic activity was determined as the reduction in writhing responses (expressed as % inhibition) caused by the test compound as compared to control responses. The analgesic activity results for the test compounds were compared to the reference drugs Aspirin and Ibuprofen.

3.4.0.0.0.0. ANTIINFLAMMATORY ACTIVITY EVALUATION

The complexity of the inflammatory process and the diversity of the drugs that have been found effective in modifying this process have resulted in the development of numerous assay methods capable of detecting antiinflammatory substances. A few of these methods have achieved popularity due to their simplicity, economic feasibility, and relative accuracy. Screening procedures that have been used in an attempt to assess the antiinflammatory potential of drugs include: (i) interference with the manifestation of one of the cardinal signs of inflammation, (ii) modification of one of the events occurring during the inflammatory process, (iii) a biological or chemical characteristic of a class of known antiinflammatory drugs, or (iv) modification of those syndromes in laboratory animals which are believed to represent models for various rheumatoid disease states.[240]

Methods based on the inhibition of an induced swelling of the rat's paw have been the most popular and the method described by Winter *et al.*[241] was used in this investigation. Test compounds suspended in gum acacia were administered orally at a dose of 100 mg/kg, one hour prior to subcutaneous injection of 0.1 mL of a 1% suspension of carrageenanan into the plantar tissue of the right hind paw and the size of the paw was measured at this time by determining the magnitude of swelling by volume displacement of mercury. Three hours and 5 hours later the size of the injected paw was again measured. Control experiments were identical except the vehicle did not contain a test compound.

Antiinflammatory activity was determined as the reduction of edema (expressed as per cent inhibition) caused by test compound with respect to a control group. The results

obtained were compared to the antiinflammatory activity exhibited by the reference drug Ibuprofen.

3.5.0.0.0.0. ULCEROGENIC LIABILITY DETERMINATION

Gastric upset and irritation are a major obstacle to patient compliance with a prescribed dosage regimen of NSAIDs. Several attempts have been made to improve gastric tolerance of NSAIDs which have met with varying degrees of success. For example, buffered, sustained-release, or enteric-coated tablets, chemical manipulation such as esterification[42] and co-administration of agents have been employed in attempts to protect the stomach.[242] Endoscopic studies, to evaluate GI injury caused by NSAIDs, have shown that 23% of patients taking NSAIDs on a regular basis, regardless of whether or not they presented GI symptoms, were found to have a significant degree of mucosal inflammation and ulceration.[159] In addition, 41% of patients with significant gastric lesions were asymptomatic.[159] NSAIDs often mask the pain associated with GI ulceration. Therefore many patients suffer dangerous complications without clinical symptoms being manifested until the problem has reached a critical stage.

It was therefore considered important to assess the ulcerogenic liability of methyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (**91a**), 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acid (**98a**), and 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (**99d**). The ulcerogenic liability of these compounds was determined according to a modified procedure reported by Nagai *et al.*[178] The results obtained for three compounds **91a**, **98a**, and **99d** were compared to that of the reference drug Ibuprofen. The results indicate that compounds **91a**, **98a**, and **99d** were completely devoid of any ulcerogenic effects at a dose of 1200 mg/kg po for a single oral dose 8 h after administration. A subsequent rat chronic study showed that **98a**, administered at a 600 mg/kg po dose, twice a day for 6 days was also completely devoid of any gastric irritation or ulcerogenicity, whereas Ibuprofen exhibited ulcerogenicity effects

in rat (UD_{50} = 250 mg/kg po). The UD_{50} for Ibuprofen was 124.6 mg/kg po dose as reported in the literature. However a different procedure was used for the determination of UD_{50} of Ibuprofen in this study.

4.0.0.0.0.0. EXPERIMENTAL

4.1.0.0.0.0. PHYSICAL CONSTANTS AND SPECTROSCOPY

Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined for solutions in deuterochloroform ($CDCl_3$) or dimethylsulfoxide-d_6 (DMSO-d_6), with a Bruker AM-300 spectrometer using tetramethylsilane (Me_4Si) as internal standard. High resolution mass (exact mass) spectra (HRMS) were recorded with an AEI MS-50 spectrometer and, in most cases, these exact mass determinations are used in lieu of elemental analyses. Infrared (IR) spectra were taken either neat, or as KBr pellets, on a Nicolet 5DX FT spectrophotometer. Microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of Alberta. pH measurements were performed using an Orion Model SA520 digital pH meter.

4.2.0.0.0.0. CHROMATOGRAPHY

Column chromatography was performed using silica gel (Merck type 7734, 100-200 mesh). Preparative thin layer chromatography (TLC) was performed with Camag Kieselgel DF-5 plates, 1.00 mm in thickness, activated at 120°C overnight prior to use. The purity of products and monitoring of reaction progress were determined using E. Merck precoated silica gel "G" microslides (250 μm in thickness). The spots were detected by shortwave ultraviolet light and/or iodine vapor visualization.

4.3.0.0.0.0. SOLVENTS AND REAGENTS

Tetrahydrofuran (THF) and diethyl ether were dried over sodium-benzophenone and distilled immediately prior to use. Benzene and acetonitrile were dried by distillation from calcium hydride. All organometallic reagents were purchased in "sure-sealed" containers from the Aldrich Chemical Company. 3-Benzoylpyridine, ethyl 3-pyridylacetate, methyl 2-

bromoacetate, methyl DL 2-bromopropionate and Evan's reagent (4S)-(-)-4-isopropyl-2-oxazolidinone were also obtained from Aldrich.

4.4.0.0.0.0. SYNTHETIC CHEMISTRY

4.4.1.0.0.0. Methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]-acetates and Methyl 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates (90-93). General Procedure A

A solution of 3-benzoylpyridine (2.0 g, 10.9 mmol, **87**) and either methyl bromoacetate (2.5 g, 16.4 mmol) or methyl DL-2-bromopropionate (2.6 g, 16.4 mmol) in anhydrous acetone (20 mL) was refluxed for 8 h to afford the respective N-substituted 3-benzoylpyridinium salts (2.6 g, 71%, **88**) and (2.8 g, 73%, **89**). A solution of **88** (1 g, 3 mmol) or **89** (1.5 g, 4.3 mmol) in dry THF (50 mL) and cuprous iodide (0.06 g, 0.3 mmol) was stirred under a nitrogen atmosphere until the solution became homogeneous. The reaction mixture was cooled to -23°C using a dry ice-CCl_4 bath. A solution of the respective Grignard reagent (phenyl, *p*-chlorophenyl, benzyl, *p*-tolyl, cyclohexyl, *n*-butyl, or iso-butylmagnesium chloride or bromide (9.6 mmol) in THF (2 M) was added dropwise and the reaction mixture was maintained at -23°C for 30 min. The reaction mixture was allowed to warm to 25°C, the mixture was stirred for 1.5 h and then a saturated aqueous solution of NH_4Cl (5 mL) was added to quench the reaction. Diethyl ether (30 mL) was added, the organic phase was separated and washed successively with solutions of 30% NH_4OH; saturated aqueous NH_4Cl (3:1 v/v, 20 mL), water (2 × 10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$) and the solvent was removed *in vacuo*. The respective products **90-93** were purified by elution from a silica gel column using an EtOAc:hexane gradient going from 5:95 to 15:85 v/v as eluent. The IR and ^1H NMR spectral data for compounds **90-93** are presented in Table 2, the physical and pharmacological data are presented in Tables 3 and 4 respectively.

4.4.1.1.0.0. *o*-Methoxyphenyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (96)

Sodium hydride (0.024 g, 1 mmol), washed with hexane to remove the mineral oil, was added slowly with stirring to a solution of guaiacol (0.98 g, 8 mmol) in dry THF (15 mL) at 20°C under a nitrogen atmosphere and the mixture was stirred for 45 min. To the resulting solution, a solution of 2-bromopropionyl bromide (1.7 g, 8.0 mmol) in dry THF (2 mL) was added dropwise and the reaction was allowed to proceed for 30 min prior to addition of ice water (10 mL). Diethyl ether (20 mL) was added, the organic phase separated and dried with anhydrous magnesium sulphate. Removal of the solvent *in vacuo* afforded the guaiacol ester **94** (1.9 g, 95%). A solution of 3-benzoylpyridine (1 g, 5.4 mmol, **87**) in acetone (25 mL) and **94** (1.0 g, 3.9 mmol) was refluxed for 24 h to give the quaternary salt **95** (1.6 g, 67%). A solution of **95** (1.6 g, 3.6 mmol) in dry THF (25 mL) and cuprous iodide (0.32 g, 1.7 mmol) was stirred under a nitrogen atmosphere at 25°C for 30 min, and the reaction mixture was cooled to -23°C using a dry ice-CCl_4 bath. A solution of phenylmagnesium chloride (0.5 g, 3.7 mmol) in THF (2.2 mL of a 2 M solution) was added dropwise and the reaction mixture was maintained at -23°C for 30 min. The reaction mixture was allowed to warm to 25°C, stirred 1.5 h, after which saturated aqueous NH_4Cl (10 mL) was added to quench the reaction. Diethyl ether (20 mL) was added, the organic phase was separated, and washed successively with solutions of 30% NH_4OH:saturated aqueous NH_4Cl (3:1 v/v, 20 mL), water (2 × 20 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo* to afford an oil which was purified by silica gel column chromatography using EtOAc:hexane (15:85, v/v) as eluent to afford **96** as an oil (0.48 g, 30%). The IR and ^1H NMR spectral data for **96** are presented in Table 2.

4.4.2.0.0.0. 2-[1-(3-Benzoyl-4-substituted-1,4-dihydropyridyl)]acetic Acids and 2-Methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic Acids (97-98). General Procedure B

Aqueous sodium hydroxide (10 mL, 1% w/v, 0.75 mmol) was added dropwise to a solution of the respective methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)acetates (0.75 mmol) (**90-91**) in ethanol:water (4:1 v/v, 12.5 mL) at 25°C with stirring. The reaction was allowed to proceed with stirring until micro TLC indicated that the reaction was complete (2 h). Removal of the solvent *in vacuo*, addition of water (10 mL) to the solution and acidification with 5 N HCl afforded a yellow solid which was filtered and dried in a drying pistol to afford the acids.

These acids (**97-98**) were characterized as their methyl ester derivatives by addition of a solution of excess diazomethane in methanol at 25°C with stirring. The respective methyl ester products were obtained in quantitative yield. The ^{1}H NMR spectra of the esters prepared in this way were identical to the corresponding esters synthesized using General Procedure A. The IR and ^{1}H NMR spectral data for compounds **97-98** are summarized in Table 2 and the physical data are presented in Table 3.

4.4.3.0.0.0. 2-Methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)acetamides (99). General Procedure C

A saturated solution of ammonia in methanol (10 mL) was added to a solution of **90-91** (2.7 mmol) in methanol (20 mL), the reaction flask was sealed with a rubber septum and the reaction was allowed to proceed for 48 h at 25°C with stirring. Removal of the solvent *in vacuo* gave the respective product which was purified by preparative TLC using EtOAc:hexane (3:1 v/v) as development solvent. Extraction of the band containing the product using EtOAc and removal of the solvent *in vacuo* afforded the respective product **99a-j** as solids. The spectral data are summarized in Table 2 and the physical data are presented in Table 3.

4.4.3.1.0.0. 3,5-Dibenzoylpyridine (100)

A mixture of 3,5-pyridinedicarboxylic acid (10 g, 59.9 mmol) and thionyl chloride (48.9 g, 411 mmol, 30 mL) was refluxed for 16 h. Excess thionyl chloride was removed by evaporation under reduced pressure. Dry benzene (2 × 10 mL) was added and evaporated to remove the last traces of the thionyl chloride. The residual acid chloride was dissolved in anhydrous benzene (60 mL) and to this solution, cooled to 5 to 10° (ice-NaCl bath), was added anhydrous aluminum chloride (40 g, 300 mmol) with stirring. The reaction mixture was allowed to warm to room temperature and then refluxed for 6 h. The dark brown mixture was poured cautiously onto ice and 5 N HCl (20 mL), and the solid 3,5-dibenzoylpyridine which was formed was collected by filtration (12.5 g, 73%) and dried in a drying pistol, m.p. 121.5-123.5°C (lit.[245] m.p. 123°C).

4.4.4.0.0.0. Methyl 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]-acetate (103). General Procedure D

A solution of 3,5-dibenzoylpyridine (1 g, 3.5 mmol, **100**) in anhydrous acetone (10 mL) was refluxed with methyl bromoacetate (0.80 g, 5.2 mmol) for 48 h to give the pyridinium salt (0.44 g, 29.4%, **101**). A solution of **101** (0.4 g, 1.1 mmol) in dry THF (20 mL) and cuprous iodide (0.02 g, 0.10 mmol) was stirred under nitrogen until the solution became homogeneous. The reaction mixture was cooled to -23°C using a dry ice-CCl_4 bath. A solution of phenylmagnesium chloride (0.48 g, 3.5 mmol) in THF (2 M solution) was added dropwise and the reaction mixture was maintained at -23°C for 30 min prior to warming to 25°C. The reaction mixture was stirred for 1.5 h and then a saturated aqueous solution of NH_4Cl (5 mL) was added to quench the reaction. Diethyl ether (20 mL) was added, the organic phase was separated and washed successively with solutions of 30% NH_4OH:saturated NH_4Cl (3:1 v/v, 10 mL), water (2 × 10 mL) and then brine (10 mL). The organic phase was dried ($MgSO_4$) and the solvent was removed *in vacuo* to give

a brownish oil which was purified by silica gel column chromatography using ether:hexane (30:70 v/v) as eluent to afford **103** as a yellow solid after recrystallization from ether (0.320 g, 66.6%).

A similar procedure was used to prepare methyl 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (**104**) by Grignard reduction of the 3,5-dibenzoyl-pyridinium salt **102** (0.3 g, 0.7 mmol). Compound **104** was purified by silica gel column chromatography using ether:hexane (30:70 v/v) as eluent to afford a yellow solid (0.10 g, 31.7%) after recrystallization from ether. The IR and ^{1}H NMR spectral data are summarized in Table 4 and the physical data are presented in Table 5.

4.4.4.1.0.0. 2-[1-(3,5-Dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamides (105 and 106)

A solution of **103** (0.1 g, 0.2 mmol) in methanol (10 mL) was subjected to ammonolysis according to General Procedure C to afford a yellow oil. The oil was purified on preparative silica gel TLC using EtOAc:hexane (3:1 v/v). Extraction of the band containing the product using ethyl acetate (2 × 10 mL) and removal of the solvent *in vacuo* afforded compound **105** as a yellow solid (0.08 g, 100%).

A similar procedure was used to synthesize compound **106** which was purified on silica gel preparative TLC using EtOAc:hexane (3:1 v/v) as development solvent to give a yellow solid in 85% yield.

The IR and ^{1}H NMR spectral data for **107** and **108** are summarized in Table 4 and the physical data are presented in Table 5.

4.4.4.2.0.0. 2-[1-(3,5-Dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetic Acids (107 and 108)

Compounds **107** and **108** were synthesized from **103** and **104** respectively according to General Procedure B and were obtained in 72% and 55% yields. The IR and

^{1}H NMR spectral data for **107** and **108** are summarized in Table 4 and the physical data are presented inTable 5.

4.4.4.4.3.0. Methyl 2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)-methyl]acrylate (111) and Methyl 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (112)

A solution of 3-benzoylpyridine (1.0 g, 5.5 mmol) and methyl 2-(bromomethyl)-acrylate (1.25 g, 7 mmol) in dry acetone (20 mL) was refluxed for 24 h to give the pyridinium salt **109** which was washed with ether after evaporation of the acetone *in vacuo* (0.76 g, 49%). To a solution of **109** (0.6 g, 2.1 mmol) in dry THF (20 mL), cuprous iodide (0.03 g, 0.2 mmol) was added and the mixture was stirred under a nitrogen atmosphere for 30 min. The reaction mixture was cooled to -23°C using a dry ice-CCl_4 bath, a solution of phenylmagnesium chloride (5.6 mmol of a 2 M solution) in THF was added dropwise and the reaction was carried out according to General Procedure A for 1 h to afford a brownish oil. Purification of this oil by preparative TLC using EtOAc:hexane (1:3, v/v) as development solvent afforded **111** as a yellow oil (R_f 0.6, 0.320 g, 42%).

Similarly, 3,5-dibenzoylpyridine (1.5 g, 5.2 mmol, **100**) was quaternized with methyl 2-(bromomethyl)acrylate (1.25 g, 7 mmol) to give the corresponding 3,5-dibenzoyl-pyridinium salt **110** which was washed with ether (20 mL) after evaporation of acetone *in vacuo* (0.9 g, 45%). To a solution of **110** (0.6 g, 1.6 mmol) in dry THF (20 mL), cuprous iodide (0.03 g, 0.2 mmol) was added and the mixture was stirred for 30 min. The reaction mixture was cooled to -23°C, a solution of phenylmagnesium chloride (5.6 mmol of a 2 M solution) in THF was added dropwise and the reaction was continued according to General Procedure A for 1 h to give a brownish oil. This oil was purified by preparative TLC using EtOAc:hexane (1:3, v/v) as the development solvent to afford **112** as a yellow oil (R_f 0.4, 0.28 g, 39%). The spectral data for **113** are presented in Table 7 and the physical data are presented in Table 8.

4.4.4.4.0.0. Methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydropyridyl)acetate (113)

To a solution of **91b** (0.5 g, 1.4 mmol) in ethyl acetate (10 mL) in a pressure bottle, 20 mg of % Pd/C was cautiously added and the reaction was allowed to proceed in the presence of hydrogen gas at a pressure of 30 psi with shaking, for 24 h at 25°C until hydrogen uptake ceased. Filtration and then removal of the solvent *in vacuo* afforded a yellow oil which was purified by preparative silica gel TLC using EtOAc:hexane (1:1, v/v) as development solvent to afford **113** as an oil (R_f = 0.65, 200 mg, 47%). The spectral data for **113** are presented in Table 7 and the physical data are presented in Table 8.

4.4.4.5.0.0. Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dibromo-2-azabicyclo[4.1.0]hept-3-ene]acetate (125) and Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dichloro-2-azabicyclo[4.1.0]hept-3-ene]acetate (126)

Phenyl(tribromomethyl)mercury (1.3 g, 2.6 mmol) was added to a stirred solution of **91b** (0.9 g, 2.6 mmol) in dry benzene (20 mL) under a nitrogen atmosphere, and the mixture was refluxed for 8 h. Additional aliquots of $PhHgCCBr_3$ (1.3 g, 2.6 mmol) were added to the reaction mixture at 2, 4, and 6 h. The reaction mixture was then cooled to 25°C and the PhHgBr which precipitated during the reaction was removed by filtration. Evaporation of the solvent *in vacuo* gave a brownish oil which was purified by preparative TLC on silica gel plates using EtOAc:hexane (1:3, v/v) as development solvent to give **125** as an oil (R_f = 0.5, 0.46 g, 50%). The oil was crystallized from hexane:ether (4:1, v/v).

Compound **126** was synthesized employing the same procedure using phenyl(bromodichloromethyl)mercury ($PhHgCBrCl_2$) and **91a**. The product obtained was purified by preparative TLC using EtOAc:hexane (1:3, v/v) as development solvent to afford an oil which was crystallized from hexane:ether (3:1, v/v) to give **126** as a solid (R_f = 0.3, 0.15

g, 33%). The spectral data for **125** and **126** are presented in Table 9 and the physical data is summarized in Table 10.

4.4.4.6.0.0. Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-difluoro-2-azabicyclo[4.1.0]hept-3-ene)]acetate (127) and Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-chloro-7-fluoro-2-azabicyclo[4.1.0]hept-3-ene)]acetate (128)

Phenyl(trifluoromethyl)mercury (1.0 g, 1.1 mmol) was added to a mixture of **91a** and **91b** (0.5 g, 1.1 mmol) and dry NaI (0.65 g, 4.3 mmol) in dry dimethoxyethane (20 mL) under a nitrogen atmosphere with stirring, and the mixture was heated at 85-90°C for 2 h. Additional aliquots of $PhHgCCF_3$ (1.0 g, 1.1 mmol) were added to the reaction mixture at 2 and 4 h after initiation of the reaction which was allowed to proceed for 6 h in total reaction time. The reaction mixture was then cooled to 25°C, and the solids (PhHgI, NaF and unreacted NaI) were removed by filtration. Removal of the solvent *in vacuo* and separation of the mixture by preparative silica gel TLC using EtOAc:hexane (1:3, v/v) as developing solvent afforded **127** as a brown oil (R_f = 0.35, 0.230 g, 53%).

Similarly, compound **128** was synthesized by refluxing $PhHgCCl_2F$ (1.0 g, 2.6 mmol) with **91b** (0.5 g, 1.1 mmol) in dimethoxyethane (20 mL). The product was isolated by preparative TLC using EtOAc:hexane (1:3, v/v) as development solvent to afford **128** as an oil (Rf = 0.55, 0.260 g, 64%). The spectral data for **127** and **128** are presented in Table 9 and the physical data is summarized in Table 10.

4.4.4.7.0.0. Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (129, 7-Br; 130, 7-Cl; 131, 7-F)

To a stirred solution of **125** (0.2 g, 0.4 mmol) and a catalytic amount of azobisisobutyronitrile (AIBN), tri-*n*-butyltin hydride (0.12 g, 0.44 mmol) in benzene (20 mL) was

added in aliquots over 8 h and the reaction mixture was refluxed at 90°C overnight to afford an oil after removal of solvent *in vacuo*. The residue obtained was washed with pentane (5 × 20 mL) to remove any remaining *n*-Bu_3SnH. The product was purified by silica gel column chromatography using hexane:ether (70:30, v/v) as eluent to afford **129** in 35% yield as an oil (R_f = 0.55)

Similar reactions employing **126** and **128** afforded **130** (R_f = 0.62, 31%) and **131** (R_f = 0.7, 45%) respectively as oils. The spectral data for **129-131** are presented in Table 9 and the physical data is presented in Table 10.

4.4.4.8.0.0. 2-Methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dibromo-2-azabicyclo[4.1.0]hept-3-ene)]acetamide (132)

To a solution of **125** (0.3 g, 0.6 mmol) in methanol (10 mL), a saturated solution of ammonia in methanol (5 mL) was added and the reaction carried out according to General Procedure C. A brownish oil was obtained which was purified by preparative silica gel TLC using EtOAc:hexane (3:1, v/v) as development solvent. The band having R_f = 0.3 was extracted with ethyl acetate (20 mL) to give a yellow oil which crystallized from hexane:ether to give **132** as a solid (0.15 g, 50%). The spectral data for compound **132** is presented in Table 9 and the physical data is presented in Table 10.

4.4.4.9.0.0. 3-Benzoyl-4-phenyl-1-{1-methyl-2-oxo-2-[(4S)-4-isopropyl-2-oxazolidinonyl]ethyl}-1,4-dihydropyridine (135)

To a solution of (4S)-(-)-4-isopropyl-2-oxazolidinone (2.71 g, 21 mmol) in dry THF (30 mL), stirred at -78°C under a nitrogen atmosphere, was added a solution of *n*-butyllithium (1.34 g, 21 mmol). The reaction mixture was stirred for 30 min at -78°C prior to the addition of **133** which was prepared from **98a** (0.5 g, 1.5 mmol) and BTBO, according to the procedure reported by Takeda *et al.*[221] Suspended BTBO (460 mg, 1 mmol) in acetonitrile (10 mL) was added to a solution of **98a** (0.5 g, 1.5 mmol) and the

reaction mixture was stirred for 1 h at room temperature, after which it was added dropwise to **134** and the resulting mixture stirred for 4 h. After evaporation of the solvent under reduced pressure, the residue was extracted with ethyl acetate. The organic layer was successively washed with 4% aqueous $NaHCO_3$, HCl, water, and brine, and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residual brownish oil was purified by silica gel preparative TLC using EtOAc:hexane (1:1, v/v). The band having $R_f = 0.6$ was isolated by extraction with ethyl acetate (30 mL) and removal of the solvent *in vacuo* afforded **135** as an oil (0.2 g, 33%). ^1H NMR ($CDCl_3$) δ: 7.2-7.6 (m, 10H, phenyl hydrogens), 7.08 [7.06] (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 6.04 (d, $J_{2,6}$ = 1.5 Hz of d, $J_{5,6}$ = 7.7 Hz, 1H, H-6), 5.28 (two overlapping q, J_{CH,CH_3} = 7.1 Hz, 1H, $CH_3C\underline{H}$), 5.1 (two d, $J_{5,6}$ = 7.7 Hz of d, $J_{4,5}$ = 4.9 Hz, 1H total, H-5), 4.88 (d, $J_{4,5}$ = 4.9 Hz, 1H, H-4), 4.2-4.5 (m, 3H, oxazolidinone, -C<u>H</u>H, -CH<u>H</u>, -NC<u>H</u>), 2.28-2.44 (m, 1H, $(CH_3)_2C\underline{H}$), 1.54 [1.56] (d, J_{CH_3CH} = 7.1 Hz, 3H, CH_3CH), 0.8-1.0 (m, 6H, $(CH_3)_2CH$). Absorptions of the minor diastereomers are indicated in brackets.

4.4.4.10.0.0. N-[(1S)-1-phenethyl]-2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide Diastereomers (137a and 137b)

A suspension of BTBO (0.46 g, 1 mmol) in acetonitrile (10 mL) was added to a solution of **108** (0.43 g, 1 mmol) and pyridine (0.079 g, 1 mmol) in acetonitrile (20 mL) and the resulting solution was stirred at 25°C for 1 h. A solution of (S)-(-)-α-methylbenzylamine (0.138 g, 1 mmol) and triethylamine (0.15 g, 1 mmol) in acetonitrile (10 mL) was added. The reaction mixture was stirred for 4 h, the solvent removed *in vacuo* and the residue was extracted with ethyl acetate (15 mL). The organic layer was succesively washed with 4% aqueous $NaHCO_3$ (10 mL), 1 N HCl (10 mL), water (10 mL), and brine (10 mL) prior to drying with Na_2SO_4. The solvent was removed *in vacuo* and the residue obtained was purified by preparative silica gel TLC using hexane:EtOAc (1:1, v/v) as

development solvent. Extraction of the two bands having R_f 0.65 and 0.5 afforded **137a** and **137b** respectively as gummy solids. ^1H NMR data for **137a** and **137b** are presented in Table 11.

4.4.4.11.0.0. (S)-Methoxycarbonyl-α-methyl methyl 2-{1-[3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl]}acetate (138)

A suspension of BTBO (0.46 g, 1 mmol) in acetonitrile (10 mL) was added to a solution of **101** (0.436 g, 1 mmol) and pyridine (0.079 g, 1 mmol) in acetonitrile (10 mL) and the reaction mixture was stirred for 1 h at 25°C. A solution of (S)-(-)-methyl lactate (0.104 g, 1 mmol) and DMAP (0.134 g, 1 mmol) in acetonitrile (10 mL) was added. The reaction mixture was allowed to proceed for 8 h at 25°C prior to addition of water (10 mL). Extraction with ethyl acetate (3 × 20 mL) and isolation of the product, as described for compound **137**, gave a residue which was purified by preparative silica gel TLC using EtOAc:hexane (1:1, v/v) as development solvent. Isolation of the band having R_f = 0.63, extraction with ethyl acetate (20 mL) and evaporation of the solvent afforded **138** (0.08 g, 12%) as an oil. ^1H NMR ($CDCl_3$) δ: 7.1-7.6 (m, 15H, phenyl hydrogens), 6.94 and 6.98 (two d, $J_{2,6}$ = 1.5 Hz, 1H each, H-2, H-6), 5.69 (s, 1H, H-4), 5.24 (q, $J_{CH_3,C4}$ = 7.2 Hz, 1H, -OC<u>H</u>(CH_3)CO_2CH_3), 4.2 (q, J_{CH,CH_3} = 7.2 Hz, 1H, NC<u>H</u>CH_3), 3.76 and 3.74 (two s, 3H total, OCH_3), 1.55-1.65 (m, 6H, NCHC<u>H</u>$_3$ and -OCHC<u>H</u>$_3$).

4.4.4.12.0.0. 3-Benzoyl-4-phenylpyridine (140)

A solution of 3-benzoylpyridine (2 g, 10.9 mmol, **87**) and cuprous iodide (0.3 g, 1.6 mmol) in dry THF (60 mL) was cooled to -78°C (dry ice/acetone). Methyl chloroformate (1.02 g, 10.9 mmol) was added dropwise to the vigorously stirred solution under nitrogen. After 30 min a solution of phenylmagnesium chloride (8 mmol) in dry THF (10 mL) was added dropwise and the mixture was stirred for 30 min at -78°C, allowed to come to room temperature, and quenched with aqueous NH_4Cl solution (10 mL). Diethylether (20 mL)

was added and the organic layer was washed with 10 mL portions of 20% NH_4Cl/NH_4OH (50:50, v/v), water and brine. After drying with anhydrous magnesium sulphate, the solution was concentrated to give the crude dihydropyridine (**139**) as a viscous oil, R_f = 0.45 (1.3 g, 38.9%).

The crude dihydropyridine **139** (1.3 g, 4.1 mmol) was refluxed in toluene (50 mL) with *o*-chloranil (1.02 g, 4.2 mmol) for 5 h, the solvent was evaporated and the brownish oil obtained was chromatographed on a silica gel column using EtOAc:hexane (15:85, v/v) as eluant to afford **140** as a yellow oil (0.9 g, 83%).

^1H NMR ($CDCl_3$) δ 8.76 (d, $J_{5,6}$ = 5 Hz, 1H, H-6), 8.7 (s, 1H, H-2), 7.64 (d, $J_{5,6}$ = 5 Hz, 1H, H-5), 7.2-7.46 (m, 10H, phenyl hydrogens).

4.4.4.13.0.0. Attempted Synthesis of (4S)- or (4R)-Methyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (143)

To a solution of diisopinocampheylchloroborane (**142**) (0.45 g, 1.4 mmol) prepared according to the reported procedure,[209] in dry THF (10 mL) was added **141** (0.55 g, 1.3 mmol) under a nitrogen atmosphere. The reaction, which was monitored by TLC, was finished in 18 h. The solvent was removed *in vacuo* and the residue obtained was chromatographed using a silica gel column using EtOAc:hexane (30:70, v/v) as eluent to afford a gummy oil (0.2 g, 35%). The ^1H NMR spectrum of the isolated product indicated that it was not the desired compound **143**.

4.4.4.14.0.0. Methyl 2-methyl-2-[1-(3-phenoxy-4-phenyl-1,4-dihydropyridyl)acetate (146)

A solution of 3-phenoxypyridine (1 g, 5.8 mmol; **144**) and methyl DL-2-bromopropionate (1.2 g, 7.6 mmol) in anhydrous acetone (20 mL) was refluxed for 24 h to give a brown solid which was washed with ether (3 × 20 mL) to afford the 3-phenoxypyridinium salt **145** (1.1 g, 80%). A solution of **145** (1.0 g, 4.2 mmol) in dry THF (20 mL) and

cuprous iodide (0.05 g, 0.3 mmol) was stirred under a nitrogen atmosphere until the solution became homogeneous. The reaction mixture was cooled to -23°C using a dry ice-CCl_4 bath. Phenylmagnesium chloride (7.6 mmol) in THF (5 mL) was added dropwise and the reaction mixture was maintained at -23°C for 30 min. The reaction mixture was allowed to warm to 25°C, the mixture was stirred for 1.5 h and then a saturated aqueous solution of NH_4Cl (5 mL) was added to quench the reaction. Diethyl ether (20 mL) was added, the organic phase was separated and washed successively with a solution of 30% NH_4OH:saturated aqueous NH_4Cl (3:1, v/v) (10 mL). The organic phase was dried ($MgSO_4$) and the solvent was removed *in vacuo*. Purification of the brownish oil obtained was carried out using both silica gel and neutral alumina column chromatography during which the compound underwent extensive decomposition. The ^1H NMR spectrum of the impure product obtained exhibited the following spectrum: ^1H NMR ($CDCl_3$) δ 6.8-7.3 (m, 11H, phenyl hydrogens, H-6), 6.02 (s, 1H, H-2), 4.65-4.72 (m, 1H, H-5), 4.46 (d, $J_{4,5}$ = 4.8 Hz, 1H, H-4), 3.82-4.02 (m, 1H, C<u>H</u>-Me), 3.78 (s, 3H, OMe), 1.44 and 1.46 (two d, J_{CH,CH_3} = 7.2 Hz, 3H, CH<u>Me</u>).

4.4.5.0.0.0. Ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]acetates (149-152), Ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (146) and Ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (147). General Procedure D

Ethyl 3-pyridylacetate (0.55 g, 3.15 mmol, R^1 = H, **147**) in dry THF (30 mL) was stirred at 25°C under a nitrogen atmosphere, CuI (0.028 g, 0.2 mmol) was added, followed by the addition of phenyl chloroformate (0.57 g, 3.7 mmol). The reaction mixture was cooled to -23°C using a dry ice-CCl_4 bath and phenylmagnesium chloride (0.47 g, 3.46 mmol) in THF (0.65 mL) was added dropwise with stirring over a period of 10 min. The reaction mixture was stirred for 15 minutes more at the same temperature and

the reaction mixture was allowed to warm to 25°C with continued stirring for 1 h. A saturated solution of NH_4Cl (5 mL) was added to quench the reaction, followed by addition of ether (30 mL). This mixture was washed with 20% NH_4Cl-NH_4OH (50:50, v/v, 2 × 20 mL), water (2 × 10 mL) and then brine (10 mL). The organic fraction was dried ($MgSO_4$), filtered and the solvent was removed *in vacuo* to give a crude oily product which was purified by silica gel column chromatography using EtOAc:hexane (15:85, v/v) as eluent to afford **149** (1.1 g, 96%) as an oil. The spectral data are presented in Table 12 and the physical data are presented in Table 13.

Similarly, compounds **150**, **151**, and **152** were synthesized in yields of 75%, 82%, and 64%, respectively as oils after purification by silica gel column chromatography using EtOAc:hexane (15:85, v/v) as eluent.

Ethyl 2-methyl-3-pyridylacetate (0.55 g, 3.7 mmol, R^1 = Me, **148**) was quaternized with phenyl chloroformate (0.57 g, 3.7 mmol) and reduced with phenylmagnesium chloride (3.46 mmol) to give a brownish oil after work-up (General Procedure D). The oil was purified by silica gel column chromatography using EtOAc:hexane (15:85, v/v) as eluent to afford **153**, R_f = 0.45 (0.9 g, 64%) as an oil.

Compound **154** was synthesized from ethyl 3-pyridylacetate (0.55 g, 3.15 mmol), methyl chloroformate (0.3 g, 3.15 mmol) and phenylmagnesium chloride (3.46 mmol) according to General Procedure D. The product was purified by silica gel column chromatography using EtOAc:hexane (15:85, v/v) as eluent to afford **154** as an oil, R_f = 0.48 (0.85 g, 87%).

4.5.0.0.0.0. DETERMINATION OF THE pK_a VALUE FOR 2-METHYL-2-[1-(3-BENZOYL-4-PHENYL-1,4-DIHYDROPYRIDYL)]-ACETIC ACID (98a)

Compound **98a** (0.33 g, 1 mmol) was dissolved in methanol (40 mL) and the volume was adjusted to 100 mL with doubly distilled water to give a 0.01 M solution. A 50 mL

aliquot of this solution was placed in a 100 mL beaker, which in turn was placed in a constant temperature circulating water bath at 25.0 ± 0.5°C. The beaker was then covered with a rubber cork fitted with a thermometer, pH microelectrode, burette, and nitrogen inlet and outlet tubes.

Purified nitrogen (freed from oxygen and carbon dioxide by passage through an alkaline solution of pyrogallol) was continuously passed through the solution to be titrated to maintain an inert atmosphere. To this solution was added carbonate-free 0.10 M methanolic potassium hydroxide (as the titrant, obtained from Anderson Laboratories, Inc., USA) in ten equal portions, each a tenth of an equivalent and the pH was recorded as soon as equilibrium was reached after each addition. The pH meter was equipped with a combined microelectrode which was calibrated before use each time, with two buffer solutions of pH 4.00 and 10.00 ± 0.01 (from BHD Chemicals). The pK_a was calculated using the Henderson-Hasselbach equation and the results are presented in Table 8.

4.6.0.0.0.0. ANALGESIC ACTIVITY ASSAY

Analgesic activity was determined using the method described by Fukawa *et al.*[239] Five male Sprague-Dawley rats, weighing between 120-150 g, were used for each test dose. The number of writhing responses induced in each rat after injection of a 4% w/v sodium chloride solution at a dose of 1 mL/kg ip were recorded two hours prior to administration of the test compound. The test compound was administered as a solution in physiological saline solution (0.9%, w/v aqueous NaCl) solubilized with 10% v/v Tween 80.

After administration of the test dose, each rat was again injected with 4% sodium chloride (1 mL/kg ip) at intervals of 30 and 60 minutes from the time the test compound was administered. The number of writhing responses elicited at each time was recorded. The lower of the two responses at the 30 or 60 minute interval was subtracted from the initial number of control writhing responses and the percentage inhibition, which is a

measure of analgesic activity, was calculated using the formula shown below. Single dose test results are reported as the mean % inhibition ± standard error of the mean (SEM) for five animals.

$$\% \text{ Inhibition } = \frac{W_1 - W_2}{W_1} \times 100$$

Where W_1 is the number of initial (control) writhing responses and W_2 is the lower of the numbers of writhing responses at either 30 or 60 minutes.

4.7.0.0.0.0. ANTIINFLAMMATORY ACTIVITY ASSAY

Antiinflammatory activity was measured using the carrageenan-induced rat paw edema assay described by Winter *et al.*[241] Four male Sprague-Dawley rats weighing 100-120 g were used in each group. Test compounds were administered as suspensions in water, using gum accaia as the suspending agent. The test compound was administered orally at a dose of 100 mg/kg one hour prior to subcutaneous injection of carrageenanan (0.1 mL, 1%) in physiological saline under the plantar skin of the right-hand paw. Control experiments were identical except the vehicle did not contain a test compound. The volume of the injected paw was measured immediately (V^1) and at 3 h and 5 h (V^2) and the % inhibition of inflammation, which is a measure of antiinflammatory activity, was calculated using the formula shown below.

$$\% \text{ Inhibition } = \frac{V^2 - V^1}{V^1} \times 100$$

4.8.0.0.0.0. ULCEROGENIC LIABILITY ASSAY

Six male Sprague-Dawley rats weighing 100-120 g, fasted for 24 h, were sacrificed 8 h after oral administration of the selected test compounds **91a**, **98a** or **99d** at doses of 300 mg/kg, 600 mg/kg and 1200 mg/kg. The stomach, sternum and duodenum were removed and macroscopically and microscopically assessed for the presence or absence of lesions which were used to calculate the UD_{50} (the dose of compound causing lesions in 50% of

the animals). A chronic ulcerogenesis assay was also performed on compound **98a** by administration of 600 mg/kg po twice daily for six days. The ulcerogenic liability assay was also used to determine the UD_{50} for the reference drug Ibuprofen.

5.0.0.0.0.0. REFERENCES

1. Sarett, L. H.; Patchet, A. A.; Steelman, S. L. The Effects of Structural Alterations on the Antiinflammatory Properties of Hydrocortisone. *Prog. Drug Res.*, **1963**, *5*, 13-26.
2. Lombardino, J. In *Nonsteroidal Antiinflammatory Drugs*, Wiley Interscience, John Wiley & Sons: New York, **1985**.
3. Wright, V.; Amos, R. Do Drugs Change the Course of Rheumatoid Arthritis? *Br. Med. J.*, **1980**, *280*, 964-966.
4. Borgeat, P.; Sirois, P. Leukotrienes: A Major Step in the Understanding of Immediate Hypersensitivity Reactions. *J. Med. Chem.*, **1981**, *24*, 121-127.
5. Stenson, W.F.; Parker, C. W. Monohydroxyeicosatetraenoic Acids (HETEs) Induce Degranulation of Human Neutrophils. *J. Immunol.*, **1980**, *124*, 2100-2104.
6. Camp, R. D. R.; Coutts, A. A.; Greaves, M. W.; Kay, A. B.; Walport, M. J. Responses of Human Skin to Intradermal Injections of Leukotrienes C_4, D_4 and B_4. *Br. J. Pharmacol.*, **1983**, *80*, 497-502.
7. Buckler, J. W.; Adams, S. S. The Phenylalkanonic Acids - Laboratory and Clinical Studies. *Med. Proc.*, **1968**, *14*, 574-578.
8. Adams, S. S.; Cliffe, E. E.; Lessel, B.; Nicholson, J. S. Some Biological Properties of Ibufenac, a New Anti-rheumatic Drug. *Nature*, **1963**, *200*, 271-272.
9. Adams, S. S.; McCullough, K. F.; Nicholson, J. S. The Pharmacological Properties of Ibuprofen, an Antiinflammatory, Analgesic and Antipyretic Agent. *Arch. Int. Pharmacodyn. Ther.*, **1969**, *178*, 115-129.
10. Van Giessen, C. J.; Kaiser, D. G. GLC Determination of Ibuprofen [dL-2-(*p*-isobutylphenyl)propionic acid] Enantiomers in Biological Specimens. *J. Pharm. Sci.*, **1985**, *64*, 798-801.

11. Kaiser, D. G.; Van Giessen, C. J.; Reicher, R. J., Wetcher, J. Isomeric Inversion of Ibuprofen (R)-Enantiomer in Humans. *J. Pharm. Sci.*, **1976**, *65*, 269-273.

12. Oralesi, G.; Selteri, R.; Volpato, I.; Innocenti, F.; Colome, J.; Sacristan, A.; Varez, G. Ibuproxam and Ibuprofen, A Pharmacological Comparison. *Arzneimittelforsch*, **1977**, *27*, 1066-1012.

13. Oralesi, G.; Mari, F.; Bertol, E.; Selleri, R.; Pisatuso, G. Antiinflammatory Agents: Determination of Ibuproxam and its Metabolite in Humans. *Arzneimittelforsch*, **1980**, *30*, 1607-1609.

14. Adams, S. S.; McCullough, K. F.; Nicholson, J. S. Some Biological Properties of Flubiprofen, an Antiinflammatory, Analgesic and Antipyretic Agent. *Arzneimittelforsch*, **1975**, *25*, 1786-1791.

15. Crook, D.; Collins, A. J.; Bacon, P.A.; Chan, R. Prostaglandin Synthetase Activity from Human Rheumatoid Synovial Microsomes. Effect of "Aspirin-Like Therapy" *Ann. Rheum. Dis.*, **1976**, *35*, 327-331.

16. Allais, A.; Roussecui, G.; Deract, R.; Benzoni, J.; Chifflot, L. Dérivés de la Série des Acides Benzoylphényl Acétiques Antiinflammatories et Analgésique. *Eur. J. Med. Chem.*, **1974**, *9*, 381-389.

17. Harrison, T. T.; Lewis, B.; Nelson, P.; Rooks, W.; Roszkwoski, A.; Tomolonis, A.; Fred, J. H. Nonsteroidal Antiinflammatory Agents I. 6-Substituted 2-Naphthylacetic Acids. *J. Med. Chem.*, **1970**, *13*, 203-205.

18. Reynolds, P. M. G.; Whorwell, P. J. A Single-Blind Crossover Comparison of Fenoprofen, Ibuprofen and Naproxen in Rheumatoid Arthritis. *Current Med. Res. Opin.*, **1974**, *2*, 461-464.

19. DeStevens, G. In: *Antiinflammatory Agents*, Academic Press, New York, Chap. 1, p. 107, **1974**.

20. Shen, T. Y. Perspectives in Nonsteroidal Antiinflammatory Research. *Angew Chem. (Int. Ed. Eng.)*, **1972**, *11*, 460-472.

21. Kuehn, F. A.; Dougherty, H. W.; Ham, E. A.; Humer, J. L.; Egan, R. W.; Winter, C. A. A Special Symposium on Indoprofen, *9th European Congress of Rheumatol.*, **1979**, Sept. 6-7, Germany.

22. Shen, T. Y.; Winter, C. A. Chemical and Biological Studies of Indomethacin, Sulindac and Their Analogs, *Advances in Drug Research*, **1977**, *12*, 89-96.

23. Hoogsteen, K.; Trenner, N. R. The Structure and Conformation of the *cis* and *trans* Isomers of 1-(*p*-chlorobenzylidene)-2-methyl-5-ethoxyindenyl Acetic Acid. *J. Org. Chem.*, **1970**, *35*, 521-523.

24. Reckenberg, H. K. In: *Phenylbutazone*, H. K. Reckenberg ed., Chap. 1, pp. 25-36, Edward Arnold, London, **1962**.

25. Brodie, B. B.; Yü, T. F.; Burns, J. J., Chenkin, T.; Patton, B. C.; Steele, J. M.; Gulman, A. B. Observations on G-25-671, A Phenylbutazone Analogue. *Proc. Soc. Exp. Biol. Med.*, **1954**, *86*, 884-886.

26. Burns, J. J.; Yü, T. F.; Ritterband, A.; Perel, J. M.; Gutman, A. B.; Brodie, B. B. A Potent New Uricosuric Agent, The Sulfoxide Metabolite of the Phenylbutazone Analogue, G-25671. *J. Pharmacol. Exp. Ther.*, **1957**, *119*, 478-426.

27. De Stevens, G. 7th International Symposium Med. Chem., Torrenolinos, Spain, **1980**.

28. Beardwell, A. Special Symposium on Indoprofen, 9th European Congress of Rheumatology, Wiesbaden, Germany, Sept. 6-7, **1979**.

29. Burns, J. J.; Yü, T. F.; Dayton, P. G.; Berger, L.; Gutman, A. B.; Brodie, B. B. Relationship between pK_a and Uricosuric Activity in Phenylbutazone. *Nature*, **1958**, *182*, 1162.

30. Gutman, A. B.; Dayton, P. G.; Yü, T. F.; Berger, L.; Chen, W.; Sicam, L. E.; Burns, J. J. A Study of the Inverse Relationship between pK_a and Rate of Renal Excretion of Phenylbutazone Analogs in Man and Dog. *Am. J. Med.*, **1960**, *29*, 1017-1033.

31. Perel, J. M.; Snell, M. M.; Chen, W.; Dayton, P. G. A Study of Structure Activity Relationships in Regard to Species Differences in the Phenylbutazone Series. *Biochem. Pharmacol.*, **1964**, *13*, 1305-1317.

32. Brodie, B. B.; Hogben, C. A. M. Some Physicochemical Factors in Drug Action. *J. Pharm. Pharmacol.*, **1957**, *9*, 345-379.

33. Bloom, B. M.; Laubach, G. D. The Relationship Between Chemical Structure and Pharmacological Activity. *Ann. Rev. Pharmacol.*, **1962**, *2*, 67-108.

34. Burns, J. J.; Yü, T. F.; Dayton, P. G.; Gutman, A. B.; Brodie, B. B. Biochemical Pharmacological Considerations of Phenylbutazone and its Analogues. *Ann. N. Y. Acad. Sci.*, **1960**, *86*, 253-262.

35. Dayton, P. G.; Berger, L.; Yü, T. F.; Sicam, L. E.; Landrau, M. R.; Gutman, A. B.; Burns, J. J. Relationship between pK_a and Renal Excretion of Various Analogues. *Fed. Proc.*, **1959**, *18*, 382.

36. Brogden, R. N.; Heel, R. C.; Speight, T. M.; Avery, G. S. Piroxicam: A Review of its Pharmacological Properties and Therapeutic Efficacy. *Drugs*, **1981**, *22*, 165-187.

37. Bachman, F. In Rheumatology in the Eighties, An Advance in Therapy - Piroxicam, (Boyle, ed.), Exceptar Medica, Princeton, **1980**.

38. Lombardino, J.; Wiseman, E. H. The Oxicams: A New Class of Nonsteroidal Antiinflammatory Agents. *Trends Pharmacol. Sci.*, **1981**, 132-134.

39. Evans, D.; Williamson, W. R. N. Chemistry of Clinically Active Antiinflammatory Compounds. *Clinical Pharmacology*, **1987**, *9*, 193-302.

40. Kumar, P.; Knaus, E. E. Synthesis and Antiinflammatory Activity of N-substituted Dihydropyridylacetic Acids, Esters and Amides. *Drug Design and Delivery*, **1987**, *2*, 145-149.

41. Kumar, P.; Knaus, E. E. Synthesis and Antiinflammatory Activity of 2*H*-Tetrazol-2-Acetic Acids, Esters and Amides. *Drug Design and Delivery*, **1990**, *6*, 169-175.

42. Whitehouse M. W.; Rainsford, K. D. Esterification of Acidic Antiinflammatory Drugs Suppresses Their Gastrotoxicity Without Adversely Affecting Their Anti-inflammatory Activity in Rats. *J. Pharm. Pharmacol.*, **1980**, 795-796.

43. Kumar, P.; Knaus, E. E. Synthesis and Antiinflammatory Activity of 5-(1,4-Dihydropyridyl)tetrazol-2-Acetic Acids, Esters and Amides. *Drug Design and Delivery*, **1991**, *7*, 287-294.

44. Higgs, G. A.; Flower, R. J.; Vane, J. R. A New Approach to Antiinflammatory Drugs. *Biochem. Pharmacol.*, **1979**, *28*, 1959-1961.

45. Higgs, G. A.; Eakins, K. E.; Mugridge, K. G.; Moncador, S.; Vane, J. R. The Effects of Nonsteroidal Antiinflammatory Drugs on Leukocyte Migration in Carageenan Induced Inflammation. *Eur. J. Pharmacol.*, **1980**, *66*, 81-86.

46. Higgs, G. A.; Mugridge, K. G.; Vane, J. R. Inhibition of Tissue Damage by the Arachidonate Lipoxygenase. *Proc. Natl. Acad. Sci. USA*, **1984**, *81*, 2890-2892.

47. Mullicam, M. D.; Wilson, M. W.; Connor, D. T.; Kostlan, C. R.; Schrier, D. J.; Dyer, R. 5-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1,3,4-Oxadiazoles and 1,2,4-Triazoles as Non-ulcerogenic Antiinflammatory Agents. *203rd ACS National Meeting, Division of Medicinal Chemistry*, San Francisco, CA, Abstract no. 121, April 5-10, **1992**.

48. Boschelli, D. H.; Connor, D. T.; Bornemeier, D. A.; Dyer, R. D.; Kuipers, P. J.; Wright, C. D. Conversion of Nonsteroidal Antiinflammatory Drugs into Dual Inhibitors of 5-Lipoxygenase and Cyclooxygenase or into Selective Inhibitors of 5-Lipoxygenase. *203rd ACS National Meeting, Division of Medicinal Chemistry*, San Francisco, CA, Abstract No. 123, April 5-10, **1992**.

49. Bender, P. E.; Newton, J. F., Jr.; Griswold, D. E.; Schmidt, S. J.; Razgaitis, K.; Adams, J. L.; Gallagher, T. F. 197th ACS National Meeting, Division of Medicinal Chemistry, Dallas, Texas, April 9-14, **1989**.

50. Appleby, C. A.; Wittenberg, B. A. Iron and Essential Component of Lipoxygenase. *J. Biol. Chem.*, **1973**, *249*, 3183-3186.

51. Corey, E. J.; Cashman, J. R.; Kantner, S. S.; Wright, S. W. Rationally Designed, Potent Competitive Inhibitors of Leukotriene Biosynthesis. *J. Am. Chem. Soc.*, **1984**, *106*, 1503-1504.

52. Jackson, W. P.; Islip, P. J.; Knean, G.; Pugh, A.; Wates, P. J. Acetohydroxamic Acids as Potent, Selective Orally Active 5-Lipoxygenase Inhibitors. *J. Med. Chem.*, **1988**, *31*, 499-500.

53. Flynn, D.; Capiris, T.; Cefanko, W. J.; Connor, D. J.; Dyer, R. D.; Kustlan, C. R.; Nies, D. E.; Schrier, D. J.; Sircar, J. C. Nonsteroidal Antiinflammatory Drug Hydroxamic Acids - Dual Inhibitors of both Cyclooxygenase and 5-Lipoxygenase. *J. Med. Chem.*, **1990**, *33*, 2070-2072.

54. Kreft, A. F.; Musser, J. H.; Kubrak, D. M.; Banlur, A. L.; Marshall, L. A.; Carlson, R. P.; Sturm, R.; Holloway, D.; Bosella, L.; Heaslip, R.; Grimes, D.; Weichman, B.; Chang, J. Y. *199th ACS National Meeting, Medicinal Chemistry Division,* Boston, Massachusetts, April 22-27, **1990**.

55. Darson, W.; Willoughby, D. A. In Acidic Nonsteroidal Antiinflammatory Drugs (Lombardino, J. G., ed.), John Wiley and Sons, New York.

56. Kline, R. L.; Scott, J. B.; Haddy, F. J.; Grega, G. J. Mechanism of Edema Formation in Canine Forelimbs by Locally Administered Bradykinin. *Am. J. Physiol.*, **1973**, *225*, 105-106.

57. Vane, J. R.; Ferreira, S. H. Interaction between Bradykinin and Prostaglandins. *Life Sci.*, **1975**, *16*, 804-805.

58. Williams, T. J. The Role of Prostaglandins in Inflammation. *Ann. R. Coll. Surg. Eng.*, **1978**, *60*, 198-200.

59. Holt, P. J. L. In: *Inflammation: Handbook of Experimental Pharmacology*, 50/2 (Vane, J. R.; Ferreira, S. H., eds.), Springer-Verlag, Berlin, p. 740, **1979**.

60. Bird, H. A.; Wright, V. Analgesic and Nonsteroidal Antiinflammatory Drugs, Applied Drug Therapy of the Rheumatic Diseases. Wright PSG, Bristol, pp. 62-87, **1982**.

61. Florey, H. W. In General Pathology (Florey, H. W., ed.), Lloyd-Luke, Ltd., London, p. 40, **1970**.

62. Dean, R. T. Macrophages as Sources of Hydrolases and other Materials in Chronic Inflammation. *Eur. J. Rheum. Inflamm.*, **1979**, *3*, 11-16.

63. Dumonde, D. C.; Glynn, L. E. The Production of Arthritis in Rabbits by an Immunological Reaction. *Br. J. Exp. Pathol.*, **1962**, *43*, 373-383.

64. Hurley, J. V.; Ryan, G. B.; Friedman, A. The Mononuclear Response to Intrapleural Injection in the Rat. *J. Pathol. Bacteriol.*, **1966**, *97*, 575-587.

65. Spector, W. G.; Walters, M. N. I.; Willoughby, D. A. The Origin of the Mononuclear Cells in Inflammatory Exudates Induced by Fibrinogen. *J. Pathol. Bateriol.*, **1965**, *90*, 181-192.

66. Unanul, E. R.; Beller, D. I.; Lu, C. T.; Alley, P. M. Antigen Presentations: Comments on its Regulation and Mechanism. *J. Immunol.*, **1984**, *132*, 1-5.

67. Glynn, L. E. The Chronicity of Inflammation and its Significance in Rheumatoid Arthritis. *Ann. Rheum. Dis.*, **1968**, *278*, 105-121.

68. Chang, Y. H.; Dearson, C. M.; Abbe, C. Adjuvant Polyarthritis: Induction by a Synthetic Adjuvant: Immunologic, Histopathologic, and Other Studies. *Arthritis Rheum.*, **1980**, *23*, 62-71.

69. Shen, T. Y. In: *Nonsteroidal Antiinflammatory Drugs* (Grattini, S.; Dukes, M. N. G., eds.), Exerpta. Med. Found., New York, p. 13, **1965.**

70. Bekemeir, H.; Bohm, R.; Hagen, V.; Hannig, E.; Henkel, H. J. Hirschelman, R.; Wenzel, U. Structure-Activity Relationship in Nonsteroidal Antiinflammatory Agents, Including QSAR in Fenamate Derivatives. *Trends in Inflammation Research*, **1981**, *2*, 19-33.

71. Gund, P.; Shen. T. Y. A Model for the Prostaglandin Synthetase Cyclo-oxygenation Site and its Inhibition by Antiinflammatory Arylacetic Acids. *J. Med. Chem.*, **1977**, *20*, 1146-1152.

72. Shen, T. Y. Prostaglandins and Inflammation. *Agents and Actions. Supplement*, **1979**, *6*, 177-185.

73. Appleton, R. A.; Brown, K. In Arachidonic acid Metabolism in Inflammation and Thrombosis. *Agents and Actions, Supplement*, **1979**, *4*, 188-192.

74. Peterson, D. A.; Gerrard, J. M.; Rao, G. H.R.; White, J. G. Inhibition of Ferrous Iron Induced Oxidation of Arachidonic acid by Indomethacin. *Prostaglandins and Medicine*, **1979**, *2*, 97-108.

75. Peterson, D. A.; Gerrard, J. M.; Rao, G. H.R.; Mills, E. L.; White, J. G. Interaction of Arachidonic Acid and Heme Iron in the Synthesis of Prostaglandins. *Prostaglandins and Thromboxane Res.*, **1980**, *6*, 157-161.

76. Egan, R. W.; Gale, P. H.; Baptista, E. M.; Kennicott, K.; VandenHewel, W. J.A.; Walker, R.; Fargerness, P. E.; Kuehle, F. A., Jr. Oxidation Reactions by Prostaglandin Cyclooxygenase Hydroperoxidase. *J. Biol. Chem.*, **1981**, *256*, 7352-7361.

77. Hayaishi, O. Oxygen Free Radicals and Tissue Damage. *Ciba Found. Symp. 65, Exerpta Medica*. Amsterdam-Oxford-New York, **1979**, 141-142.

78. Shen, T. Y. Nonsteroidal Antiinflammatory Agents. *Burger's Medicinal Chemistry*, 4th Ed., Wolf, M. E., ed., John Wiley and Sons, Toronto, Part III, pp. 1205-1271, **1981**.

79. Foye, W. O. *Principles of Medicinal Chemistry*, 2nd ed., Lea and Febiger, Philadelphia, **1981**, Chap. 22, pp. 561-590.

80. Ariens, E. J. In Stereochemistry and Biological Activity of Drugs, Timermans, P. B. M. W. M., ed., Bladwell, London, **1983**, Chap. 22, pp. 11-31.

81. Ariens, E. J. Stereochemistry, A Basis for Sophisticated Nonsense in Pharmacokinetics and Clinical Pharmacology. *Eur. J. Clin. Pharmacol.*, **1984**, *26*, 663-668.

82. Cyaen, M. N. Racemic Mixtures and Single Stereoisomers: Industrial Concerns and Issues in Drug Development. *Chirality*, **1991**, *3*, 94-98.

83. Bertucci, C.; Rossini, C.; Pini, D.; Salvadori, P. Chiral Stationary Phases and Circular Dichroism Detection in High-Performance Liquid Chromatography: Determination of Stereochemical Purity. *J. Pharm. Biomed. Anal.*, **1987**, *5*, 171-176.

84. Hutt, A. J.; Caldwell, J. The Metabolic Chiral Inversion of 2-Arylpropionic Acids - A Novel Route with Pharmacological Consequences. *J. Pharm. Pharmacol.*, **1983**, *35*, 693-704.

85. Day. R. O.; Graham, G. G.; Williams, K. M.; Champion, G. D.; DeJager, J. Clinical Pharmacology of Nonsteroidal Antiinflammatory Drugs. *Pharmacol. Ther.*, **1987**, *33*, 383-433.

86. De Camp, H. FDA Perspective on the Development of Stereoisomers. *Chirality*, **1989**, *1*, 2-6.

87. Roth, H. J.; Kleenman, A.; Beiswenger, T. *Pharmaceutical Chemistry*, Vol. I, Drug Synthesis, Ellis Horwood, Chichester, England, p. 249, **1988**.

88. Foltrest, W. H., Jr.; Colin, R.; Brown, C. R.; Shroff, P. F.; Teutsh, G. Relative Potency of Propiram and Morphine for Analgesia in Man. *J. Clin. Pharmacol.*, **1972**, *12*, 440-448.

89. Heel, R. C.; Brogden, R. N.; Speight, T. M.; Avery, G. S. Disopyramide: A Review of its Pharmacological Properties and Therapeutic Use in Treating Cardiac Arrythmias. *Drugs*, **1978**, *15*, 331-368.

90. Klayman, D. L.; Bartosevich, J. F.; Griffin, T. S.; Mason, C. J.; Scovill, J. P. 2-Acetylpyridine Thiosemicarbazones 1. A New Class of Potential Antimalarial Agents. *J. Med. Chem.*, **1979**, *22*, 855-862.

91. Medical Subject Headings, Supplementary Chemical Records, 1984, National Library of Medicine, Bethesda, MD, 83, 572, Nov. **1983**.

92. Betterfield, J. L.; Wright, G. C.; Chang, Y. C. Hypotensive Property of 3-Amino-2-hydrazinopyridine hydrochloride. *Fed. Proc.*, **1978**, *37*, 353.

93. Pavia, M. R.; Taylor, C. P.; Lobbestael, S. J. 6-Alkyl-N,N-Disubstituted-2-pyridinamines as Anticonvulsant Agents. *J. Med. Chem.*, **1989**, *32*, 1237-1242.

94. Smits, J. F. M.; Struyker-Boudier, H. A. J. Preferential Renal Vasodilator Effects of CGP 22979A in Concious Spontaneously Hypertensive Rats. *J. Pharmacol. Exp. Ther.*, **1985**, *232*, 845-849.

95. Robertson, D. W.; Beedle, E. E.; Swartzendruber, J. K.; Jones, N. D.; Elzey, T. K.; Kauffman, R. F.; Wilson, H.; Hayes, J. S. Bipyridine Cardiotonics: The Three-Dimensional Structures of Amrinone and Milrinone. *J. Med. Chem.*, **1986**, *29*, 635-640.

96. Bruce, T. C.; Benkovic, S. J. Nicotinamide Nucleotides. *Bioorganic Mechanisms*, **1966**, *2*, 301-343.

97. Meyer, H.; Bossent, F.; Valin, W.; Stoepel, K.; Towant, R. German Patent, 2, 45, 530, May 8, 1980, Chem. Abstr. 93, 1501236, **1980**.

98. Balogh, M.; Hernecz, I.; Meszaros, Z.; Simon, K.; Puxztay, L.; Horvalt, G.; Dvortsak, P. Studies in Chemotherapeutics, Synthesis of 5-Substituted-4-oxo-1,4-dihydro-3-pyridine Carboxylic Acid Derivatives. *J. Heterocyclic Chem.*, **1980**, *17*, 359-368.

99. Ross, W. C. J. The Preparation of Some 4-Substituted Nicotinic Acids and Nicotinamides. *J. Chem. Soc., C.*, **1966**, 1816-1821.

100. Phillips, A. P. Hantzsch's Pyridine Synthesis. *J. Am. Chem. Soc.*, **1949**, *71*, 4003-4007.

101. Cook. A. H.; Heilbron, I. M.; Steger, L. New Therapeutic Agents of the Quinoline Series Part IV. Lutidylquinolines. *J. Chem. Soc.*, **1943**, 413-417.

102. Inone, Y.; Matsumoto, T.; Niwa, H.; Suzuki, K.; Hoshide, Y. Pat. Appl. 87156 (Eur.), Chem. Abstr., 100, 6530 **1984**.

103. Suzuki, K.; Shiraishi, T.; Yosida, Y.; Matumoto, T.; Iwamoto, M.; Motoyshi, Y.; Niwa, H.; Inone, Y. Pat. Appl. 118120 (Eur.), Chem. Abstr., 102, 45961, **1985**.

104. Majore, A.; Kopylova, T. N.; Salvada, L.; Dubur, G.; Ogle, Z.; Uldrikis, J. *Eksper. Med.*, **1982**, *14*, 197.

105. Goncharova, R. I.; Kuzhir, T. D.; Dubur, G.; Ogle, Z.; Uldrikis, J. *Dokl. Akad. Nauk. SSSR*, **1980**, *255*, 1483-1485.

106. Fanta, C. H.; Lacoutuse, J. W.; Drazen, J. M. *In-vivo* Bronchodilator Activity of Nifedipine in the Guinea Pig. *Am. Rev. Respir. Dis.*, **1987**, *136*, 76.

107. Sunkel, C. E.; Fau de Casa Juana, M.; Santos, L.; Mar Gamez, M.; Villarroya, M.; Gonzales-Moralez, M. A.; Priego, J. G.; Ortega, M. P. 4-Alkyl-1,4-dihydro-pyridine Derivatives as Specific PAF-Acether Antagnoists. *J. Med. Chem.*, **190**, *33*, 3205-3210.

108. Archibald, J. L.; Bradley, G.; Opalko, A.; Ward, T. J.; White, J. C.; Ennis, C.; Shepperson, N. B. Design of Antithrombotic-Antihypertensive Agent ($W_4$27569). Synthesis and Evaluation of a Series of 2-Heteroaryl-substituted Dihydropyridines. *J. Med. Chem.*, **1990**, *33*, 646-652.

109. Panten, U.; Zielmann, S.; Schrader, M. T.; Lenzen, S. The Dihydropyridine Derivative Bay K8644 Enhances Insulin Secretion by Isolated Pancreatic Islets. *Naun. Schmeid. Arch. Pharmacol.*, **1985**, *328*, 351-353.

110. Malaise, W. J.; Mathias, P. C. Stimulation of Insulin Release by an Organic Calcium Agonist. *Diabetologia*, **1985**, *28*, 153-156.

111. Fischer, W.; Mueller, M. Zur Beein Flussung der Effektivität Einiger Antiepileptika Durch Ca^{2+}-Kanalblocker und Referenzsubstanzen beim Maximalen Elektrokrampf der Maus. *Pharmazie*, **1987**, *42*, 420-421.

112. Bossert, F.; Meyer, H.; Wehinger, E. 4-Aryldihydropyridines, A New Class of Highly Active Calcium Antagonists. *Angew. Chem. Int. Ed. Engl.*, **1981**, *20*, 762-769.

113. Akula, M. R.; Matowe, W. C.; Wolowyk, M. W.; Knaus, E. E. Synthesis and Calcium Channel Antagonist Activity of 3-Arylmethyl 5-Isopropyl-1,4-dihydro-2,6-dimethyl-4-(pyridyl)-3,5-pyridinedicarboxylate. *Pharm. Res.*, **1990**, *1*, 919-922.

114. Bodor, N.; Alim, A. Improved Delivery Through Biological Membranes. XIX. Novel Redox Carriers for Brain-Specific Chemical Delivery Systems. *J. Pharm. Sci.*, **1985**, *74*, 241-243.

115. Bodor, N.; Pep, E.; Anderson, W.; Vlasak, J.; Brewster, M. E. *203rd ACS National Meeting, Medicinal Chemistry Division*, San Francisco, CA, Abstract No. 41, April 5-10, **1992**.

116. Kumar, R.; Ji, G.; Wiebe, L. I.; Knaus, E. E. Synthesis of Brain Targeted 5-Iodo-5-Vinyl and (E)-5-(2-Iodovinyl)-2'-Deoxyuridine Coupled to a Dihydropyridine Pyridium Salt Redox Chemical Delivery System. *J. Heterocyclic Chem.*, **1991**, *28*, 711-715.

117. Phelan, M. J.; Bodor, N. Improved Delivery Through Biological Membranes XXXVII. Synthesis and Stability of Novel Redox Derivatives of Naproxen and Indomethacin. *Pharm. Res.*, **1989**, *6*, 667-676.

118. Lyle, R. E. In Heterocyclic Compounds. Pyridine and its Derivatives. Supplement to Volume 14, Part 1, p. 137 (Abramovitch, R. A., ed.), John Wiley and Sons Inc., **1974**.

119. Eisner, U.; Kuthan, J. The Chemistry of Dihydropyridines. *Chem. Rev.*, **1972**, *42*, 1-42.

120. Kuthan, J.; Kurfurst, A. Development in Dihydropyridine Chemistry. *Ind. Engl. Chem. Prod. Res. Dev.*, **1982**, *21*, 191-261.

121. Sausins, A.; Duburs, G. Synthesis of 1,4-Dihydropyridines by Cyclocondensation Reactions. *Heterocycles*, **1988**, *27*, 269-289.

122. Sausins, A.; Duburs, G. Synthesis of 1,4-Dihydropyridines in Cyclocondensation Reactions. *Chemistry of Heterocyclic Compounds*, **1992**, *28*, 363-391.

123. Lyle, R. E.; Gautier, G. J. Reactions of Nucleophiles with Pyridinium Ions. Cyanide Reactions with Some Pyridinium Ions. *Tetrahedron Lett.*, **1965**, 4615-4621.

124. Stout, D. M.; Meyers, A. I. Recent Advances in the Chemistry of Dihydropyridines. *Chem. Rev.*, **1982**, *82*, 223-243.

125. Fowler, F. W. Synthesis of 1,2- and 1,4-Dihydropyridines. *J. Org. Chem.*, **1972**, *37*, 1321-1323.

126. Sundberg, R. J.; Hamilton, G.; Trindle, C. Synthesis and Diels-Alder Reactions of the N-Carbalkoxydihydropyridines. Substituent Effects on the Regiochemistry of Reduction of N-Carbalkoxypyridinium Ions. *J. Org. Chem.*, **1986**, *51*, 3672-3679.

127. (a) Abramovitch, R. A.; Poulton, G. A. Aromatic Substitution. Part XXII. Reactions of Some 3-Substituted Pyridines with Alkyl-Lithium Compounds. *J. Chem. Soc. B.*, **1969**, 901-903. (b) Abramovitch, R. A.; Giam, C. S. Competitive Reactions of Pyridines, 3-Picoline and 3-Ethyl Pyridine with Phenyl-Lithium. Activation of Nucleophilic Aromatic Substitution by Allyl Groups. *Can.*

J. Chem., **1964**, *42*, 1627-1637. (c) Abramovitch, R. A.; Helmer, F.; Leveris, M. Kinetics of Nucleophilic Substitutions of Some Bromopyridines and Picolines with Thiophenoxide Ion. Nature of Activation by ortho-Methyl Groups. *J. Org. Chem.*, **1969**, *34*, 1730-1734.

128. Knaus, E. E.; Redda, K. The Sodium Borohydride Reduction of N-Sulfonylpyridinium Salts. Synthesis of N-Sulfonyl-1,4-(1,2-)dihydropyridines. *Can. J. Chem.*, **1977**, *55*, 1788-1791.

129. Houton, R. F.; Westheimer, F. H. N-Methyldihydronicotinamide. *Tetrahedron*, **1958**, *3*, 73-77.

130. Comins, D. L.; Abdullah, A. H. Synthesis of 1-Acyl-1,4-dihydropyridines via Copper Hydride Reduction of 1-Acylpyridinium Salts. *J. Org. Chem.*, **1984**, *49*, 3392-3393.

131. (a) Akiba, K.; Matsuoka, H.; Wada, M. Regiospecific Introduction of Alkyl Groups to the 4-Position of Pyridines. *Tetrahedron Lett.*, **1981**, *22*, 4093-4096. (b) Akiba, K.; Iseki, Y.; Wada, M. Regiospecific Synthesis of 4-Alkyl Pyridines via 1,4-Dihydropyridine Derivatives. *Tetrahedron Lett.*, **1982**, *23*, 429-436. (c) Akiba, K.; Iseki, Y.; Wada, M. Facile Synthesis of 4-Substituted Pyridines using Grignard Reagents. *Tetrahedron Lett.*, **1982**, *23*, 3935-3936.

132. Piers, E.; Soucy, M. Reaction of Cuprate Reagents with Pyridine in the Presence of Chloroformate. A Novel Synthesis of 1,4-Dihydropyridines. *Can. J. Chem. Soc.*, **1974**, *52*, 3563-3564.

133. (a) Katritzky, A. R.; Beltrami, H.; Sammes, M. Preparation of 4-Aryl and 4-Heteroaryl Pyridines: Regiospecific Nucleophilic Attack γ- to a Quaternary Nitrogen Atom. *J. Chem. Soc. Chem. Commun.*, **1979**, 137. (b) Katritzky, A. R.; Belbrami, H.; Keay, J. G.; Rogers, D. N.; Sammes, M. P.; Leung, C. W.; Lee, C. M. Regiospecific Nucleophilic Attack at the γ-Position of 1-(2,6-Dimethyl-

4-oxo-1,4-dihydro-1-pyridyl) Pyridinium Compounds: Novel Synthesis of 4-Substituted Pyridines. *Agnew Chem. Int. Ed. Engl.*, **1979**, *18*, 792.

134. Comins, D. L.; Abdullah, A. H. Regioselective Addition of Grignard Reagents to Aryl Pyridinium Salts. A Convenient Method for the Synthesis of 4-Alkyl(aryl)pyridine. *J. Org. Chem.*, **1982**, *47*, 4315-4319.

135. Dubey, S. K.; Knaus, E. E. Solvent and Temperature Effects on the Nucleophilic Addition of Organolithiums to 3-(4,4-Dimethyloxazolin-2-yl)pyridine. *Heterocycles*, **1986**, *24*, 125-134.

136. (a) Frankel, G.; Cooper, J. W.; Fink, C. M. One-Step Synthesis of 2-Substituted N-Ethoxycarbonyl-1,2-dihydropyridine. *Angew. Chem. Int. Ed. Engl.*, **1970**, *9*, 523. (b) Lyle, R. E.; White, E. The Reaction of Organometallic Reagents with Pyridinium Ions. *J. Org. Chem.*, **1971**, *36*, 772-777.

137. Thiessen, L. M.; Lepoivre, J. A.; Alderwieseldt, F. C. Preparation of 1,2,4-Trialkyl or Aryl Substituted 1,2-Dihydropyridine by Grignard Reagents. *Tetrahedron Lett.*, **1974**, *1*, 59-62.

138. (a) Lyle, R. E.; Comins, D. L. Regioselective Nucleophilic Addition to 3,4-Lutidine. *J. Org. Chem.*, **1976**, *41*, 3250-3251. (b) Lyle, R. E.; Marshall, J. L.; Comins, D. L. The Reaction of 1-Arylpyridinium Salts with Grignard and Organocadmium Reagents. *Tetrahedron Lett.*, **1977**, 1015-1018.

139. Hauck, A. E.; Giam, G. S. Regioselective Nucleophilic Addition of Organo-Lithium Compounds to 3-(4,4-Dimethyloxazolin-2-yl)pyridine. *J. Chem. Soc.*, **1980**, *207*, 2076.

140. Sonawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni, D. G. Recent Developments in the Synthesis of Optically Active α-Arylpropanoic Acids: An Important Class of Nonsteroidal Antiinflammatory Agents. *Tetrahedron: Asymmetry*, **1992**, *3*, 163-191.

141. (a) Horner, L.; Siefel, H.; Buthe, H. Asymmetric Catalytic Hydrogenation with an Optically Active Phosphine Rhodium Complex in Homogeneous Solutions. *Angew. Chem. Int. Ed. Engl.*, **1968**, *7*, 942. (b) Knowles, W. S.; Sabacky, M. J. Catalytic Asymmetric Hydrogenation Employing a Soluble Optically Active Rhodium Complex. *J. Chem. Soc. Chem. Commun.*, **1968**, 1445-1446. (c) Noyori, R.; Nagai, K.; Kitamura, M. Asymmetric Hydrogenation of Unsaturated Carboxylic Acids Catalyzed by BINAP-Ruthenium(II) Complexes. *J. Org. Chem.*, **1987**, *52*, 3174-3178.

142. Katsuki, T.; Sharpless, K. B. The First Practical Method for Asymmetric Epoxidation. *J. Am. Chem. Soc.*, **1980**, *102*, 4974-4976.

143. Takana, T. S.; Yanase, M.; Ogasawara, K. Enantiodevergent Synthesis of Both Enantiomers of Ibuprofen from (2S, 3S)-3-Phenylglycidol. *Heterocycles*, **1989**, *29*, 1849-1853.

144. Hiyama, T.; Wakasa, N. Asymmetric Coupling of Arylmagnesium Bromides with Alkyl Esters. *Tetrahedron Lett.*, **1985**, *26*, 3259-3262.

145. Larson, R. D.; Corley, E. G.; Davis, P.; Reider, P. J.; Gabowski, J. J. α-Hydroxy Esters as Chiral Reagents: Asymmetric Synthesis of 2-Arylpropionic Acids. *J. Am. Chem. Soc.*, **1989**, 7650-7651.

146. Price, A.; Fletcher, F. Mechanisms of NSAID-Induced Gastropathy. *Drugs*, **1990**, *40*, 1-11.

147. Roth, S. H. Nonsteroidal Antiinflammatory Gastropathy Deaths and Medical Practice. *Annals of Internal Medicine*, **1987**, *109*, 353-354.

148. Armstrong, C.; Blower, A. L. Nonsteroidal Antiinflammatory Drugs and Life Threatening Complications of Peptic Ulcerating Gut. **1987**, *28*, 427-432.

149. Mitchell, D. M.; Spritz, P. W.; Young, D. J-Y.; Bloch, D. A.; McShane, D. J. Survival, Prognosis and Causes of Death in Rheumatic Arthritis. *Arthritis and Rheumatism*, **1986**, *29*, 106-114.

150. Fries, J. F.; Miller, F. R.; Spitz, P. Q. Toward an Epidemiology of Gastropathy Associated with Nonsteroidal Antiinflammatory Drug Use. *Gastroenterology*, **1989**, *96*, 647-655.

151. Graham, D. Y. Prevention of Gastroduodenal Injury Induced by Chronic Nonsteroidal Antiinflammatory Drug Therapy. *Gastroenterology*, **1989**, *96*, 675-681.

152. Robinson, D. Prostaglandins and the Mechanism of Action of Antiinflammatory Drugs. *Am. J. Med.*, **1983**, *75*, 26-31.

153. Luzzani, F.; Colombo, G.; Shiatti, P.; Selva, D.; Glasser, A. Inhibition of P. G. Production by MDL 035, a New Non-Steroidal Non-Acidic Antiinflammatory Compound, in Rat Gastric Mucosa and Inflammatory Exudate. *Pharmacol. Res. Commun.*, **1984**, *16*, 755-763.

154. Shen, T. Toward More Selective Antiarthritic Therapy. *J. Med. Chem.*, **1981**, *24*, 1-5.

155. Vane, J. R. Inhibition of Prostaglandin Synthesis as a Mechanism of Action for Aspirin-Like Drugs. *Nature (New Biol.)*, **1971**, *231*, 232-235.

156. Robert, A. Antisecretory, Antiulcer, Cytoprotective, and Diarrheogenic Protective Properties of Prostaglandins. *Adv. Prostaglandins Thromboxane Res.*, **1976**, *2*, 507-520.

157. Parker, B. M. On the Synthesis of Prostaglandins by Human Gastric Mucosa and its Modification by Drugs. *Biochem. Biophys. Acta*, **1977**, *487*, 307-314.

158. (a) Collins, P. W. Development and Therapeutic Role of Synthetic Prostaglandins in Peptic Ulcer Disease. *J. Chem.*, **1986**, *29*, 437-463. (b) Miller, T. A. Gastroduodenal Mucosal Defense: Factors Responsible for the Ability of the Stomach and Duodenum to Resist Injury. *Surgery*, **1988**, *103*, 389-397.

159. Jones, E.; Bishop, A. E. Adverse Effect of Nonsteroidal Antiinflammatory Drugs. *Drug Protocol*, **1987**, *2*, 7-11.

160. Willette, R. E. Analgesic Agents. In Textbook of Organic, Medicinal and Pharmaceutical Chemistry. Wilson & Gisvold, 8th Ed., Chapter 17, Doerge, R. F., ed., Philadelphia, J. B. Lippincott, pp. 643-645, **1982**.

161. Korolkovas, A. Essentials of Molecular Pharmacology. Background for Drug Design, Wiley, New York, p. 57, **1970**.

162. Lazer, E. S.; Wong, H-C.; Possanza, G. J.; Graham, A. G.; Farina, P. R. Antiinflammatory 2,6-Di-tert-butyl-4-(2-arylethynyl)phenols. *J. Med. Chem.*, **1989**, *32*, 100-104.

163. (a) Comins, D. L.; Monstlo, H. B. Regioselective Alkylation of 3-Bromopyridine. *J. Heterocyclic Chem.*, **1983**, *20*, 1239-1243. (b) Comins, D. L.; Stroud, E. D.; Herrick, J. J. Regioselective Addition of Grignard Reagents to the 1-Phenoxycarbonyl Salts of Alkyl Nicotinamides. *Heterocycles*, **1984**, *22*, 151-157. (c) Comins, D. L. α-Metalation of 1-(tert-Butoxycarbonyl)-1,4-Dihydropyridines. *Tetrahedron Lett.*, **1983**, *24*, 2807-2810.

164. Abramovitch, R. A.; Singer, G. M. In Pyridine and Its Derivatives. Abramovitch, R. A., ed., Wiley Interscience, New York, pp. 48-54.

165. Raban, D. J.; Rodriguez, W. Conformational Properties of Oxidation-Reduction Cofactor. *J. Am. Chem. Soc.*, **1985**, *107*, 4146-4152.

166. Karle, I. L. The Crystal Structure of N-Benzyl-1,4-dihydronicotinamide. *Acta Crystallographica*, **1961**, *14*, 497-502.

167. Glasfeld, A.; Zbinden, P.; Dobler, M.; Benner, S. A.; Dunitz, J. D. Crystal Structures of Two Simple N-Substituted Dihydronicotinamides: Possible Implications for Stereoelectronic Arguments in Enzymology. *J. Am. Chem. Soc.*, **1988**, *110*, 5152-5157.

168. Hays, G. R.; Huis, R.; Coleman, B.; Clague, D.; Verhoveven, J. W.; Rob, F. High Resolution Solid-State ^{13}C NMR Conformational Structures of NADH and NAD^+ Model Systems. *J. Am. Chem. Soc.*, **1981**, *103*, 5140-5151.

169. Meyer, W. L; Mahler, H. R.; Baker, R. M. Nuclear Magnetic Resonance Spectrum and Conformation of 1,4-Dihydropyridine. *Biochem. Biophys. Acta*, **1962**, *64*, 353-358.

170. Levy, H. R.; Vennesland, B. The Stereospecificity of Enzymatic Hydrogen Transfer from Diphosphopyridine Nucleotide. *J. Biol. Chem.*, **1958**, *228*, 85-96.

171. Nambiar, K. P.; Stauffer, D. M.; Kolodziej, P. A.; Benner, S. A. A Mechanistic Basis for the Stereoselectivity of Enzymatic Transfer of Hydrogen from Nicotinamide Cofactors. *J. Am. Chem. Soc.*, **1983**, *105*, 5886-5890.

172. Wallenteb, K.; Hoffmann, D. Über den mechanismus der wasserstoffübertragung mit pyridinnucleotiden XVIII. *Tetrahedron Lett.*, **1959**, *15*, 10-13.

173. Hoffmann, H. J.; Cimiraglia, R. Reference Conformations for Calcium Antagonists and Agonists of Dihydropyridine Type. *J. Mol. Structure (Theochem.)*, **1990**, *205*, 1-11.

174. Mager, P. P.; Coburn, R. A.; Solo, A. J.; Triggle, D. J.; Rolhe, H. QSAR, Diagnostic Statistics and Molecular Modelling of 1,4-Dihydropyridine Calcium Antagonists: A Difficult Road Ahead. *Drug Des. Discov.*, **1992**, *8*, 273-298.

175. Mukherjee, A.; Lahiri, S. C. Synthesis and Pharmacological Evaluation of Some Potential Non-Steroidal Antiinflammatory Agents with Low Gastric Irritancy. *193rd National ACS Meeting, Medical Chemistry Division*, Denver, Colorado, April 5-10, Abstract No. 43, **1987**.

176. Atul, K. *10th Int. Congress of Pharmacology*, Sydney, Australia, August 23-28, Abstract No. P515, **1984**.

177. Albert, A.; Serjeant, E. P. In The Determination of Ionization Constants, A Laboratory Manual. Chapman and Hall, pp. 14-70, **1984**.

178. Nagai, Y.; Kirio, K.; Nakamura, H.; Uno, H.; Nishimura, H. Nonsteroidal Anti-inflammatory Agents [(Heteroarylamino)phenyl]alkanoic Acids. *J. Med. Chem.*, **1987**, *26*, 222-226.

179. Bundgaard, H.; Nielsen, H. M. Esters of N,N-Disubstituted 2-Hydroxy-acetamides as a Novel Highly Biolabile Prodrug Type for Carboxylic Acid Agents. *J. Med. Chem.*, **1987**, *30*, 451-454.

180. Cioli, V.; Putzolu, S.; Rossi, V.; Corradine, C. A Toxicological and Pharmacological Study of Ibuprofen Guiaicol Ester (AF 2259) in the Rat. *Tox. Applied Pharmacol.*, **1980**, *54*, 332-339.

181. Wainer, I.; Doyle, T. D.; Adams, N. M. Liquid Chromatographic Chiral Stationary Phases in Pharmaceutical Analysis: Determination of Trace Amounts of the (-)-Enantiomer in (+)-Amphetamine. *J. Pharm. Sci.*, **1984**, *73*, 1162-1168.

182. Rubin, A.; Knalder, M. P.; Ho, P. P. K.; Betchol, L. D.; Wolen, R. L. Stereoselective Inversion of (R)-Fenoprofen to (S)-Fenoprofen in Humans. *J. Pharm. Sci.*, **1985**, *74*, 82-84.

183. Harrison, I. I.; Lewis, B.; Nelson, P.; Rooks, W.; Rosszowski, A. Nonsteroidal Antiinflammatory Agents II 6-Substituted-2-Naphthylacetic Acids. *J. Med. Chem.*, **1970**, *13*, 203-205.

184. Newton, D. W.; Murray, W. J.; Lovell, M. W. pK_a Determination of Benzhydryl-piperazine Antihistamines in Aqueous and Aqueous Methanol Solutions. *J. Pharm. Sci.*, **1982**, *71*, 1363-1366.

185. Davis, L. J. Ibuprofen, Drug Intelligence. *Clin. Pharm.*, **1975**, *9*, 501-503.

186. Linstead, R. P.; Whetstone, R. R.; Levine, P. The Stereochemistry of Catalytic Hydrogenation VI. The Hydrogenation of 9-Phenanthrol and Related Substances and the Identification of Three of the Possible Stereoisomeric Forms of the Perhydrophenanthrene Ring. *J. Am. Chem. Soc.*, **1942**, *64*, 1985-2022.

187. van Bergen, T. J.; Kellog, R. M. Ring Expansion of a 1,2-Dihydropyridine to an Azepine. *J. Org. Chem.*, **1971**, *36*, 978-983.

188. Lyle, R. E.; Mallet, S. E. The Partial Hydrogenation of Pyridines. *Ann. N.Y. Acad. Sci.* **1967**, *145*, 83-90.

189. Freidfelder, M. Hydrogenation in the Pyridine Series I. Catalytic Reduction of the Isomeric Acetylpyridines. *J. Org. Chem.*, **1965**, *29*, 2895-2898.

190. Wenkert, E.; Wickberg, B. General Methods of Synthesis of Indole Alkaloids IV. A Synthesis of DL-Eburnamonine. *J. Am. Chem. Soc.*, **1965**, *87*, 1580-1592.

191. Fossheim, R.; Svarteng, K.; Mostad, A.; Romming, C.; Stretter, E.; Triggle, D. Crystal Structures and Pharmacological Activity of Calcium Channel Antagonists 2,6-Dimethyl-3,5-dicarbomethoxy-4-phenyl-1,4-dihydropyridines. *J. Med. Chem.*, **1982**, *25*, 126-131.

192. Gordon, J. Halogenation and Olefinic Nature of Cyclopropane. *J. Chem. Ed.*, **1967**, *44*, 461-464.

193. March, J. In *Advanced Organic Chemistry. Reactions, Mechanisms and Structure*; 3rd edn., p. 131. Toronto: John Wiley and Sons Inc., **1985**.

194. Noller, C. R. In *Chemistry of Organic Compounds*; 3rd edn., p. 291. Philadelphia: W.B. Saunders Co., **1966**.

195. De Meijerre, A. Bonding Properties of Cyclopropane and Their Chemical Consequences. *Angew Chem. Int. Ed. Engl.*, **1979**, *18*, 809-826.

196. Gassman, P. G. "Twist" Bent Bonds. *Chem. Commun.*, **1967**, 793-795.

197. Tandon, M.; Singh, S.; Wiebe, L. I.; Knaus, E. E.; Gatti, W. P.; Tempest, M. L. Synthesis of the Diastereomers of 5-(2,2'-Dichlorocyclopropyl) and 5-(2-Chloro-cyclopropyl)-2'-deoxyuridine and the Antiviral and Cytotoxic Activity of These and Bromo Analogs. *Drug Design Del.*, **1991**, *7*, 295-307.

198. Tandon, M.; Singh, S.; Xu, L.; Kumar, P.; Wiebe, L. I.; Knaus, E. E.; Gatti, W. P.; Tempest, M. L. Synthesis and Bioloical Activity of 5-(2,2-Difluorocyclo-propyl)-2'-deoxyuridine Diastereomers. *Drug Design Del.*, **1992**, *9*, 79-91.

199. Seyferth, D.; Lambert, R. L. Halomethyl-Metal Compounds XX. An Improved Synthesis of Phenyl(tribromomethyl)mercury Compounds. *J. Organometal. Chem.*, **1969**, *16*, 21-26.

200. Seyferth, D.; Hopper, S. P. Halomethyl-Metal Compounds LX. Phenyl(trifluoromethyl)mercury: A Useful Difluorocarbene Transfer Reagent. *J. Org. Chem.*, **1972**, *37*, 4070-4075.

201. Karplus, M. Comments on the Signs of Proton Coupling Constants. *J. Am. Chem. Soc.*, **1962**, *84*, 2458-2460.

202. Bell, J. A. The Properties and Reactivity of Methylene: Derived Principally from the Gas-Phase Reactions. *Prog. Phys. Org. Chem.*, **1964**, *2*, 1-61.

203. Moss, R. A. Carbonic Selectivity in Cyclopropanation Reactions. *Acc. Chem. Res.*, **1980**, *2*, 58-64.

204. Schoeller, W. W.; Aktekin, N.; Friege, H. Olefin Selectivities in the Addition of Carbenes. *Angew. Chem. Int. Ed. Engl.*, **1982**, *21*, 932-933.

205. Moss, R. A.; Perez, L. A.; Turro, N. J.; Gould, I. R.; Hacker, N. P. Hammet Analysis of Absolute Carbene Addition Rate Constants. *Tetrahedron Lett.*, **1983**, *24*, 685-688.

206. Skell, P. S.; Garner, A. Y. Reactions of Bivalent Carbon Compounds. Reactivities in Olefin-Dibromocarbene Reactions. *J. Am. Chem. Soc.*, **1956**, *78*, 5430-5433.

207. Doering, W. E.; Henderson, W. A. The Electron-seeking Demands of Dichlorocarbene in its Addition to Olefins. *J. Am. Chem. Soc.*, **1958**, *80*, 52-74, 5276.

208. Woodworth, R. C.; Skell, P. S. Methylene, CH_2. Stereospecific Reaction with *cis* and *trans*-2-Butene. *J. Am. Chem. Soc.*, **1959**, *81*, 3383-3386.

209. Jones, M.; Ando, W.; Hendrick, M. E.; Kulczyki, A.; Howley, P. M.; Hummenl, K. F.; Malamert, D. S. Irradiation of Methyl Diazomalonate in Solution. Reactions of Singlet and Triplet Carbenes with Carbon-Carbon Double Bonds. *J. Am. Chem. Soc.*, **1972**, *94*, 7469-7479.

210. Giese, B.; Lee, W-B.; Neuman, C. Evidence for Intermediates in the Cycloaddition of Singlet Carbenes. *Angew. Chem. Int. Ed. Engl.*, **1982**, *21*, 310.

211. March, J. In: *Advanced Organic Chemistry. Reactions, Mechanisms and Structure*, 3rd ed; John Wiley & Sons: New York, p. 975, **1985**.

212. (a) Seyferth, D.; Yamazaki, H.; Alleston, D. L. Stepwise Reduction of gem-Dihalocyclopropane with Tri-*n*-butyltin Hydride. *J. Org. Chem.*, **1963**, *28*, 703-706. (b) Horton, D.; Priebe, W.; Sznaidman, M. L. Steric and Conformational Effects in the Dehalogenation of 2-Halo Sugar Derivatives with Tributylstannane. *J. Org. Chem.*, **1993**, *58*, 1821-1826.

213. Jackman, L. M.; Sternhell, S. In Applications of Nuclear Magnetic Resonance Spectrometry in Organic Chemistry, 2nd ed.; Pergamon Pres: Toronto, pp. 228-229 and 286, **1969**.

214. Tandon, M.; Wiebe, L. I.; Knaus, E. E. Synthesis, Separation and Absolute Configuration of the Two 5-(2,2-dibromocyclopropyl) and four 5-(2-bromocyclopropyl) Diastereomers of 2'-Deoxyuridine. *Can. J. Chem.*, **1989**, *67*, 1484-1488.

215. Giordano, C.; Castaldi, G.; Gavichioli, S.; Villa, M. A Stereoconvergent Strategy for the Synthesis of Enantiomerically Pure (R)-(-) and (S)-(+)-2-(6-methoxy-2-naphthyl)propionic Acid (Naproxen). *Tetrahedron*, **1989**, *45*, 4243-4252.

216. Ahmar, M.; Girard, C.; Block, R. Enzymatic Resolution of Methyl-2-Alkyl-2-arylacetates. *Tetrahedron Lett.*, **1989**, *30*, 7053-7056.

217. Baird, J. M.; Kern, J. R.; Lee, G. R. An Investigation of the Palladium-Catalyzed Formate-Mediated Hydroxycarbonylation of Optically Active 1-Arylethyl Esters. *J. Org. Chem.*, **1991**, *56*, 1933.

218. Miles, W. H.; Smiley, P. M.; Brinkman, H. R. The Reaction of Chiral Nucleophiles with Organomanganese Arene Complexes. *J. Chem. Soc. Chem. Commun.*, **1989**, 1897-1899.

219. Fadel, A. Optically Active Arylpropionic Acids from the Stereoselective Alkylation of Chiral Imide Enolates. *Synlett*, **1992**, *No. 1*, 48-50.

220. Gonzáles, A. Asymmetric Synthesis of 2-Arylpropionic Acids. *Synthetic Commun.*, **1991**, *21*, 1353-1360.

221. Takeda, K.; Tsuboyama, K.; Yamaguchi, K.; Ogura, H. 1,1'-Bis[6-(trifluoromethyl)benzotriazolyl]oxalate (BTBO): A New Reactive Coupling Reagent for the Synthesis of Dipeptides, Esters and Thioesters. *J. Org. Chem.*, **1985**, *50*, 273-275.

222. Naruto, S.; Terada, A. Optical Resolution of (±)-2-[4-(2-Oxocyclohexylidenemethyl)phenyl]propionic Acid. *Chem. Pharm. Bull.*, **1991**, *39*, 190-191.

223. Buckle, D. R.; Arch, J. R. S.; Fenwich, A. E.; Houge-Frydrych, C. S.; Pinto, I. L.; Smith, D. G.; Taylor, S. G.; Tedeer, J. M. Relaxant Activity of 4-Amido-3,4-dihydro-2H-12-benzopyran-3-ols and 4-Amido-2H-1-benzopyrans on Guinea Pig Isolated Trachealis. *J. Med. Chem.*, **1990**, *33*, 3028-3034.

224. Ogliaruso, M. A.; Wolfe, J. F. In The Chemistry of Acid Derivatives. Patai, S. ed. Wiley: New York, Chapter 7, pp. 270-462, **1979**.

225. Gross, H.; Bilk, L. Zur Reaction von N-hydroxysuccinimid mit Dicyclohexylcarbochiimid. *Tetrahedron*, **1968**, *24*, 6935-6939.

226. Ueda, M.; Oikawa, H.; Takuma, T. 1,1'-[Carbonyldioxy]dibenzotriazole: A New, Reactive Condensing Agent for the Synthesis of Amides, Esters and Dipeptides. *Synthesis*, **1983**, 908-909.

227. Itoh, M.; Hagirawa, D.; Notani, J. A Simple and Mild Esterificaton Method for Carboxylic Acids Using Sulfonate-type Compound Reagents. *Synthesis*, **1975**, 456-458.

228. Srebnik, M. S.; Ramachandran, P. V.; Brown, H. C. Chiral Synthesis via Organoboranes. 18. Selective Reductions 43 Diisopirocampheylchloroborane as an Excellent Chiral Reducing Reagent for the Synthesis of Halo Alcohols of High

Enantiomeric Purity. A Highly Enantioselective Synthesis of Both Optical Isomers of Tomoxetine, Fluoxetine, and Nisoxetine. *J. Org. Chem.*, **1988**, *53*, 2916-2920.

229. Chandrasekharan, J.; Ramachandran, P. V.; Brown, H. C. Diisocampheylchloroborane, A Remarkably Efficient Chiral Reducing Agent for Aromatic Prochiral Ketones. *J. Org. Chem.*, **1985**, *50*, 5446-5448.

230. Rieu, J-P.; Boucherpe, A.; Cousse, H.; Mouzin, G. Methods for the Synthesis of Antiinflammatory 2-Arylpropionic Acids. *Tetrahedron*, **1986**, *42*, 4095-4110.

231. Renshaw, R. R.; Conn, R. C. Pyridyl Ethers and Pyridinium Salts. *J. Am. Chem. Soc.*, **1937**, *54*, 297-301.

232. Jacob, J. J. C.; Ramabadran, K. Stereospecific Effects of Opiate Antagonist on Superficial and Deep Nociception on Motor Activity Suggests Involvement of Endorphins on Different Opioid Receptor. *Life Sci.*, **1979**, *24*, 1959-1970.

233. Loux, J.J.; Smitts, S. Salem, H. Comparative Analgesic Testing of Various Compounds in Mice Using Writhing Techniques. *Arzeneim. Forsch.*, **1978**, *28*, 1644-1647.

234. Giesler, G. J.; Lieberkind, J. Inhibition of Visceral Pain by Electrical Stimulation of the Periaqueductal Gray Matter. *Pain*, **1976**, *2*, 43-48.

235. Hendershot, L. C.; Forsaith, J. Antagonism of the Frequency of Phenylquinone-Induced Writhing in the Mouse by Weak Analgesics and Non-analgesics. *J. Pharmacol. Exp. Ther.*, **1959**, *125*, 237-240.

236. Collier, H. O. J.; Dineen, L. C.; Johnson, C. A.; Schneider, C. The Abdominal Constriction Response and its Suppression by Analgesic Drugs in the Mouse. *Br. J. Pharmacol. Chemother.*, **1968**, *32*, 295-310.

237. Burns, R. B. P.; Alioto, J. .; Hurley, K. E. A. A Modification of the Bradykinin-Induced Writhing Test for Analgesia. *Arch. Int. Pharmacodyn.*, **1968**, *175*, 41-53.

238. Lim, K.S.; Guzman, F.; Sakurac, A.; Cahn, J.; Charpentier, J. (eds.), *Pain*. pp. 119-152, London: Academic Press, **1968**.

239. Fukawa, K.; Kawano, O.; Hibi, M.; Misaka, N.; Ohba, S.; Hatanaka, Y. A Method for Evaluating Analgesic Agents in Rats. *J. Pharmacol. Methods*, **1980**, *4*, 251-259.

240. Swingle, K. F. In *Antiinflammatory Agents*; Scherner, R.; House, M. (eds.), Chap. 2, pp. 33-34, London: Academic Press, **1974**.

241. Winter, C. A.; Risley, E. A.; Nuss, G. W. Carageenan-Induced Edema in Hind Paw of the Rat as an Assay for Antiinflammatory Drugs. *Proc. Soc. Exp. Biol. Med.*, **1962**, *111*, 544-547.

242. Leyck, S.; Dereu, N.; Etschenberg, E.; Glyczy, M.; Graf, E.; Winkelmann, J.; Parnham, M.J. Improvement of the Gastric Tolerance of Nonsteroidal Antiinflammatory Drugs by Polyene Phosphatidylcholine (Phospholipon® 100).

243. Hamor, G. H. Nonsteroidal Antiinflammatory Drugs. In *Principles of Medicinal Chemistry*, Foye, W.O. (ed.), Chap. 23, pp. 520 and 525, 3rd Edn. Philadelphia: Lea and Febiger, **1989**.

244. Hamor, G. H. Nonsteroidal Antiinflammatory Drugs. In *Principles of Medicinal Chemistry*, Foye, W.O. (ed.), Chap. 22, pp. 580, 2nd Edn. Philadelphia: Lea and Febiger, **1981**.

245. Poirier, R. H.; Morin, R. D.; McKin, A.M.; Bearse, A. E. Abnormal Condensation of Piperidinium Acetate with Aromatic Aldehydes. *J. Org. Chem.*, **1961**, *26*, 4275-4278.